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ACUTE PHASE REACTANTS

I. SERUM NONGLUCOSAMINE POLYSACCHARIDES IN PATIENTS WITH RHEUMATIC FEVER AND RELATED CONDITIONS

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DURING the acute phase of disease, remarkable nonspecific changes occur in the blood serum. The term "acute phase reactants" is used in this series of publications to designate those substances whose serum levels are characteristically altered under such circumstances. This terminology is employed analogously to the use of the term "acute phase protein" in referring to the "C-reactive protein" originally described by Tillett and Francis[1] and studied extensively by Ash[2] Abernethy and Avery,[3] MacLeod and Avery,[4] and Anderson and McCarty.[5]

Not only protein substances but likewise other substances, including carbohydrates, may demonstrate behavior characteristic of acute phase reactants. Normal serum contains polymeric carbohydrate complexes in both albumin and globulin fractions.[6] The concentration of these polysaccharides is increased in the serum of patients with tuberculosis,[7-9] malignancies,[7, 8, 10-15] acute pneumonia,[10, 16] toxemic pregnancy,[17, 18] acute bacterial infections[17] and a variety of miscellaneous conditions including hepatic cirrhosis, nephrosis, arthritis, cholelithiasis, ulcerative colitis, and pemphigus.[14] This variety of circumstances which bring about elevations in the serum polysaccharide levels justifies the designation of the serum polysaccharides as acute phase reactants.

Various acute phase reactants have been demonstrated[19-24] to exhibit characteristic elevations of their serum levels in patients with rheumatic fever and related diseases. In only a few such patients have observations of elevations in serum polysaccharide levels been reported.[14, 17] Since it seemed probable that a systematic investigation of serum polysaccharides in patients with rheumatic fever and related diseases might reveal a characteristic pattern of response, this study was undertaken.

MATERIALS AND METHODS

Serum nonglucosamine polysaccharides were determined in triplicate according to the tryptophane method of Shetlar and associates.[25, 26] The 500 mμ wave length employed is at or near the absorption maximum for the carbohydrate-tryptophane compounds of galactose, mannose, glucose, and fructose and minimizes the effects of glucosamine and of hemoglobin since their absorption maxima are less than 400

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mμ. This method has an obvious advantage over methods previously described for the determination of serum polysaccharides in that tryptophane resulting from the hydrolysis of protein does not interfere with the reaction.

Blood specimens were obtained by venipuncture and centrifuged at 2,500 to 3,000 r.p.m. for fifteen to twenty minutes. The separated serum was stored in the frozen state until used.

Included in the study were fifty-seven patients ranging in age from 3 to 17 years and suffering with acute rheumatic fever, active juvenile rheumatoid arthritis, active lipoid nephrosis, acute glomerulonephritis, Sydenham's chorea, anaphylactoid purpura, and periarteritis nodosa. These patients were all diagnosed according to standard criteria. The diagnosis of periarteritis nodosa was made by biopsy and later confirmed at autopsy. Data obtained on thirty children with inactive rheumatic fever are included for comparison. The subjects comprising this group of patients are individuals who had been observed in a previous acute attack of rheumatic fever and who have residual cardiac murmurs but normal erythrocyte sedi-

TABLE I. SERUM POLYSACCHARIDES IN PATIENTS WITH RHEUMATIC FEVER

ACTIVE					INACTIVE*	
	INITIAL		MAXIMUM			
PT.	NGP†	ESR‡	NGP	ESR	PT.	NGP
Je. B.	169	50	174	50	M. A.	178
Ju. B.	186	48	186	53	L. B.	125
N. B.	185	46	189	51	P. B.	148
B. C.	192	52	197	52	C. C.	159
E. C.	202	55	202	55	R. C.	116
L. C.	171	47	171	49	S. C.	181
M. C.	188	40	188	49	B. D.	129
W. C.	174	51	196	56	P. E.	159
A. D.	201	54	201	54	E. F.	138
S. D.	183	45	183	60	G. F.	162
J. F.	175	51	175	51	K. G.	160
M. F.	176	57	176	57	B. H.	124
T. F.	198	52	198	53	S. H.	101
B. H.	200	54	200	56	A. I.	165
K. H.	174	46	195	55	J. K.	103
W. H.	173	57	194	58	M. K.	111
W. K.	181	46	181	54	C. L.	146
A. L.	178	55	178	55	M. M.	161
L. L.	194	55	194	55	R. N.	116
P. L.	169	50	195	50	R. N.	98
T. L.	200	59	200	59	M. P.	62
M. M.	170	54	200	57	P. R.	76
C. N.	196	42	196	42	W. R.	90
J. N.	200	58	200	58	B. S.	167
J. O.	146	43	187	52	D. S.	122
R. O.	135	34	166	49	G. S.	112
P. S.	174	52	174	53	G. W.	107
S. S.	184	51	200	52	M. W.	162
G. T.	191	44	191	52	M. W.	149
M. W.	199	54	199	54	T. W.	86
Mean	182		190			130
SEM	±2.9		±1.9			±5.8
t	20.5		15.8			2.4

*All of these patients had normal erythrocyte sedimentation rates at the time of study.
†NGP = Nonglucosamine polysaccharides in milligrams per cent.
‡Wintrobe method.

mentation rates and no clinical evidence of rheumatic activity at the time of these studies.

OBSERVATIONS

The nonglucosamine polysaccharide levels observed in patients with active and inactive rheumatic fever are shown in Table I. This table shows the initial serum nonglucosamine polysaccharide value and the maximum value obtained during the illness of those children with acute rheumatic fever. The erythrocyte sedimentation rates at corresponding times are recorded. Although in nineteen of the thirty cases studied the initial nonglucosamine polysaccharide value was the highest value obtained, in eleven individuals a further increase in this level occurred which was accompanied in eight patients by a corresponding increase in the erythrocyte sedimentation rate.

In the series of normal individuals studied by Shetlar and associates[27] the nonglucosamine polysaccharide levels were found to increase with increasing ages of the patients and no levels higher than 138 mg. per cent were found even in aged patients. Shetlar and collaborators[14] have concluded that any serum nonglucosamine polysaccharide level above 140 mg. per cent may be considered as definitely abnormal. In the present study seventy-one determinations on fifty-three normal young adults yielded a mean value of serum nonglucosamine polysaccharide concentration of 114 ± 3.2 mg. per cent. Ten of these seventy-one values were greater than 140 mg. per cent.

As is shown in Table I each of the thirty cases of active rheumatic fever showed a maximum serum nonglucosamine polysaccharide level considerably higher than 140 mg. per cent. The lowest such value obtained in any of these cases (166 mg. per cent) exceeds this level by 26 mg. per cent and exceeds the quoted maximum normal value for this age group[27] by 40 mg. per cent. The mean of the maximum levels observed during the course of the illness in these thirty patients was 190 mg. per cent, representing a highly significant difference from the control group. The initial observation of the serum nonglucosamine polysaccharide level in all cases but one revealed similar elevations. In this case the child became more acutely ill subsequent to his admission to the hospital; the worsening of his condition was reflected by an increase in the erythrocyte sedimentation rate as well as in the nonglucosamine polysaccharide level. The mean value of the initial observations of the serum nonglucosamine polysaccharide in the patients with acute rheumatic fever was 182 mg. per cent; this, likewise, represents a highly significant difference from the control group.

In the group of thirty patients with inactive rheumatic fever many but not all of the nonglucosamine polysaccharide levels observed were lower than the 140 mg. per cent value quoted[14] as the upper extreme of normal values. Seventeen of the thirty patients had levels lower than and thirteen had levels higher than this. The mean concentration of nonglucosamine polysaccharides in the serum of these patients was 130 mg. per cent, indicating a significant difference from the control group.

Serial determinations of the serum nonglucosamine polysaccharide levels were obtained throughout the course of the patient's illness in all cases of

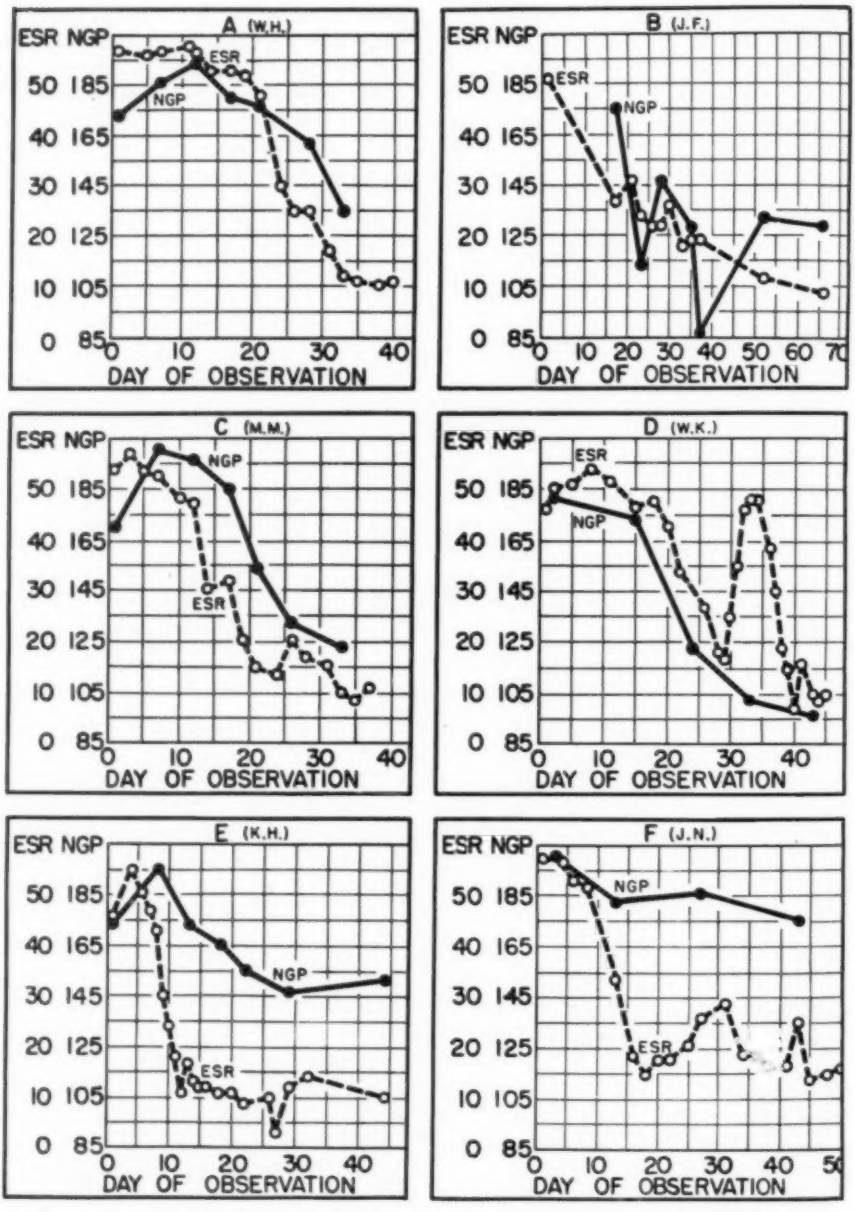

Fig. 1.—Serum nonglucosamine polysaccharides in patients with acute rheumatic fever.

acute rheumatic fever. The data obtained in six illustrative cases are shown in Fig. 1. In four of these individuals (A, B, C, D) the polysaccharide level returned to normal in a nearly parallel fashion with the erythrocyte sedimentation rate. This was the usual occurrence and was observed in most cases. However, in certain patients there appeared to be little correlation between the erythrocyte sedimentation rate and the polysaccharide level. Cases E and F represent such individuals.

TABLE II. SERUM NONGLUCOSAMINE POLYSACCHARIDES IN PATIENTS WITH DISEASES RELATED TO RHEUMATIC FEVER

PT.	INITIAL		MAXIMUM	
	NGP	ESR	NGP	ESR
Active Juvenile Rheumatoid Arthritis				
R. A.	182	44	182	44
C. K.	139	30	181	45
J. M.	156	8	190	8
G. S.	177	22	196	35
R. S.	199	44	199	44
G. W.	201	36	201	36
R. W.	161	15	161	15
J. C.	166	49	166	49
Acute Glomerulonephritis				
R. A.	203	48	203	48
S. J.	180	53	180	61
M. S.	123	45	148	56
Lipoid Nephrosis				
A. H.	158	50	158	50
K. J.	178	22	189	50
V. R.	111	52	111	52
M. W.	134	35	166	50
Sydenham's Chorea				
V. B.	103	6	103	9
B. M.	146	14	177	13
E. N.	179	42	179	42
C. B.	188	11	188	11
V. B.	120	25	180	21
L. H.	153	10	158	28
J. R.	174	18	174	18
P. A.	167	20	167	20
D. I.	170	35	170	35
J. I.	146	38	146	38
Periarteritis Nodosa				
B. B.	205	62	209	69
Anaphylactoid Purpura				
R. F.	194	48	194	48

Table II shows the nonglucosamine polysaccharide levels observed in patients suffering with diseases related to rheumatic fever. The value obtained upon the initial observation and the maximum value observed during the course of the patient's illness, as well as the erythrocyte sedimentation rates observed at corresponding times, are indicated for each patient. In the patients suffering with juvenile rheumatoid arthritis, acute glomerulonephritis, anaphylactoid purpura, and periarteritis nodosa, there were elevated serum nonglucosamine polysaccharide levels observed in every case. Of the four patients with active lipoid nephrosis, one failed to show elevated levels. Of the ten patients suffering with Sydenham's chorea, only one failed to show elevated serum concentrations of nonglucosamine polysaccharides at some time during the period of observation and eight of the ten had such elevations at the initial observation.

DISCUSSION

The demonstrations that the serum concentrations of mucoproteins,[20, 28, 29] hyaluronidase inhibitor,[30-34] C-reactive protein,[1-5] and hexosamines[10, 13, 14] are increased in a variety of acute diseases were followed by observations of similar increases of these acute phase reactants in the serums of patients suffering with rheumatic fever or related diseases.[19-24, 35] Therefore, the finding reported here of consistent, significant elevations of the serum levels of nonglucosamine polysaccharides in patients with such diseases is not an unexpected one, since several groups of investigators[7-18] have previously demonstrated that these acute phase reactants are present in increased con-

centration in the serums of patients with a variety of acute diseases.

The findings with regard to serum nonglucosamine polysaccharides in patients with Sydenham's chorea are deserving of mention. It has been a common observation that patients with Sydenham's chorea uncomplicated by exudative manifestations of rheumatic fever need not exhibit increased erythrocyte sedimentation rates. Likewise, it has been demonstrated that the hyaluronidase inhibitor[19] and the mucoprotein[20] serum levels are not elevated in this condition. The increased concentration of nonglucosamine polysaccharides in the serum of most of the patients with Sydenham's chorea reported here is, therefore, an unexpected finding, whose explanation must await further investigation.

The significance of the observations reported here is not immediately apparent. The demonstration of an adrenal mechanism[36, 37] functioning in the control of the serum levels of nonspecific hyaluronidase inhibitor and mucoproteins fosters the speculation that changes in the serum levels of other acute phase reactants may similarly reflect alterations in adrenal activity. It has been suggested by Seibert and associates[7] that the elevations of serum polysaccharide levels observed by them in certain pathological conditions are related to tissue destruction. Shetlar and co-workers,[38] on the other hand, have concluded that the elevation of serum polysaccharides is correlated with tissue proliferation rather than tissue destruction. This latter conclusion is based on the observations that following the production of experimental inflammation there is a delayed increase in serum polysaccharide level with the maximum values being observed three to six days after injury and that inflammatory processes caused by injection of talc suspensions or turpentine, conditions in which little tissue destruction is thought to occur, produce the same effect of elevation of the serum polysaccharide level. Perhaps the concept of an adrenal mechanism controlling the serum polysaccharide level with elevations in that level resulting from any of a number of nonspecific stress stimuli might reconcile these two interpretations. Investigation of this possibility is in progress.

The possibility of clinical application of the determination of serum nonglucosamine polysaccharides is worthy of consideration. The procedure is simple to perform and could well be carried out as a routine procedure by any modern clinical laboratory. This group of diseases is notoriously difficult to diagnose. It is generally conceded that with present criteria only the most florid cases are identifiable. Especially is this true with regard to rheumatic fever, rheumatoid arthritis, and periarteritis nodosa. The urgent need for additional diagnostic tools is manifest. Difficult as it may be to diagnose these diseases, the difficulty of eliminating them from a differential diagnosis is even greater. Any laboratory procedure which is capable of demonstrating consistent differences between patients with these diseases and normal individuals merits serious consideration. On the basis of existing data with regard to serum nonglucosamine polysaccharides reported here, it would appear that there is a consistent disparity between patients with rheumatic fever and re-

lated diseases and normal individuals with respect to their serum levels of these acute phase reactants. The nonspecificity of elevations of serum nonglucosamine polysaccharides obviates the possibility of employing such elevations as criteria by which to make a diagnosis of any of these diseases. However, the observation of consistent increases in the serum levels of these substances in patients suffering with any of this group of diseases suggests that the finding of a normal or subnormal nonglucosamine polysaccharide level in a given patient should militate against the diagnosis of rheumatic fever or related disease in that individual.

SUMMARY

1. Serum nonglucosamine polysaccharides were determined in fifty-seven patients with rheumatic fever or related disease in an active phase and in thirty patients with inactive rheumatic fever.

2. Elevated serum levels of these substances were observed consistently in every individual who was studied during the active phase of any of these diseases with the exceptions of one patient suffering with active Sydenham's chorea and one patient suffering with active lipoid nephrosis.

3. Many, but not all, patients with inactive rheumatic fever exhibited normal serum levels of nonglucosamine polysaccharides. Statistical analysis reveals a significant difference between the serum nonglucosamine polysaccharide levels of the inactive rheumatic fever patients studied and the control group.

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ACUTE PHASE REACTANTS

II. Serum Hexosamines in Patients With Rheumatic Fever and Related Diseases

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TWO amino derivatives of hexose-monosaccharides, glucosamine and galactosamine, exist in significant concentrations in normal and pathological human blood serums. These are known collectively as serum hexosamines and are measured as such by any of the "hexosamine" methods in common use, since all of these methods fail to differentiate between glucosamine and galactosamine. The serum hexosamines have been demonstrated to exist in the blood serum in increased concentrations during the acute phase of various diseases, including malignancies,[1, 2] infections,[1, 2, 3] rheumatic fever and related diseases,[1, 2, 4, 5] cholelithiasis, ulcerative colitis, pemphigus, benign prostatic hypertrophy,[2] and acute myocardial infarction,[1] and therefore are included in the group of substances designated as acute phase reactants.[6]

Two systematic studies of serum hexosamine levels in patients with mesenchymal diseases have appeared in the literature during the past two years. In the first of these Rosenberg and Schloss[4] studied the serum hexosamine levels in patients with acute rheumatic fever. In this study it was observed that the serum hexosamine levels were elevated during the acute phase of the disease but rapidly returned to normal with quiescence of the disease. Recently Boas and Soffer[5] have studied the serum hexosamine levels in nineteen patients with acute disseminated lupus erythematosus. Seventeen of these patients were found to have elevated serum levels of hexosamines. In contrast to these findings, Shetlar and associates[2] mention lupus erythematosus as one of a group of diseases in which no abnormalities in serum hexosamines were noted in any case studied.

Since there has been little systematic study of the serum hexosamines in rheumatic fever and related diseases and since the data that do exist are not in complete agreement, the present study was undertaken in an attempt to clarify our understanding of the response of the serum hexosamines in these diseases. In this study the serum hexosamine levels have been observed at frequent intervals throughout the course of illness in patients with rheumatic fever and various related diseases.

EXPERIMENTAL

Serum hexosamines were determined by the method of Shetlar and collaborators,[7] which is a modification of the method of Elson and Morgan.[8] All determinations were run in duplicate and serum blanks were run routinely as recommended[7] to eliminate the effect of interfering colors.

Blood for these studies was obtained by venipuncture from patients ranging in age from 3 to 17 years. The serum was separated by centrifugation for fifteen to twenty minutes at 2,500 to

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3,000 r.p.m. and was stored in the frozen state until used. Included in this study are sixty-seven patients with acute rheumatic fever, Sydenham's chorea, active juvenile rheumatoid arthritis, acute glomerulonephritis, active lipoid nephrosis, anaphylactoid purpura, and periarteritis nodosa; in addition forty patients in the convalescent phase and forty in the inactive phase of rheumatic fever are included. These diagnoses were made according to standard criteria. In the case of periarteritis nodosa the diagnosis was made at biopsy and confirmed at necropsy.

OBSERVATIONS

Serum hexosamine values obtained by the method employed range consistently lower than those obtained by the method of West and Clark[1] which was used in the studies of Rosenberg and Schloss[4] and of Boas and Soffer.[5] The data obtained in the present study by thirty-seven determinations of serum hexosamines in twenty-nine normal young adults indicate a mean serum hexosamine level of 54 ± 1.8 mg. per cent. Shetlar and co-workers[7] studied the serum hexosamines in normal individuals of various age groups and found a progressive increase in the normal values from birth to old age. Except in the aged group (61 to 85 years), the extreme upper limit of values obtained by them was 78 mg. per cent. Since the same chemical method has been employed in the present study, and since the data obtained on normal individuals are in essential agreement with those of Shetlar and associates, this value will be accepted as the upper limit of normal.

In Table I are shown the serum hexosamine levels observed in forty cases of acute rheumatic fever, forty of convalescent rheumatic fever, forty of inactive rheumatic fever, and ten of Sydenham's chorea. Of the forty individuals suffering with acute rheumatic fever, twenty-seven or 67.5 per cent had elevated serum hexosamine levels upon the initial examination. In sixteen of these 40 patients the initial hexosamine determinations yielded the highest value obtained at any time during the course of the illness. However, in twenty-four of them (60 per cent) the maximum elevation of the hexosamine level occurred at some time subsequent to this. Only three of the forty individuals failed to exhibit an abnormally high hexosamine level at some time during the course of their illnesses. Statistical analysis reveals highly significant differences between the data on the control group and those on the patients with acute rheumatic fever whether initial or maximum values obtained on the latter group be considered.

On the other hand, during the convalescent phase of the disease all individuals had normal hexosamine levels. In this instance statistical analysis revealed no significant difference between the data on the control group and on the group of patients convalescent from rheumatic fever. Among the forty individuals with inactive rheumatic fever, three had elevated hexosamine levels, and among the ten patients with Sydenham's chorea one had an elevated hexosamine level. This patient was suffering a severe attack of chorea which rendered him unable to talk, to feed himself, or to prevent himself from falling out of bed unless restrained. He had a moderate elevation of his erythrocyte sedimentation rate but no other stigmas

of exudative rheumatic fever. Statistical evaluation of the data on patients with inactive rheumatic fever reveals a significant difference and on patients with Sydenham's chorea a very significant difference from the data on the control group. However, in spite of this statistical evidence of elevation of hexosamine levels in patients with inactive rheumatic fever and with chorea the small number of individuals with abnormally high concentrations of hexosamines minimizes the significance of this finding since in the absence of pre-existing data on any given individual whose serum hexosamine concentration lies within the expected normal range it is manifestly impossible to detect minor elevations in that level as compared to his normal level.

In each of the patients with acute rheumatic fever the serum hexosamines were determined serially throughout the course of the patient's

TABLE I. SERUM HEXOSAMINES IN PATIENTS WITH RHEUMATIC FEVER

ACTIVE			CONVALESCENT		INACTIVE		CHOREA	
PT.	INIT.	MAX.	PT.	HA	PT.	HA	PT.	HA
L. A.	83	84	G. A.	63	M. A.	72	P. A.	74
Je. B.	47	90	L. A.	61	K. B.	65	C. B.	68
Ju. B.	83	105	Je. B.	64	L. B.	83	Ve. B.	59
N. B.	99	99	Ju. B.	61	P. B.	77	Vo. B.	71
B. C.	83	103	K. B.	51	R. C.	67	L. H.	73
E. C.	101	114	B. C.	40	R. C.	48	D. I.	71
L. C.	81	81	Ba. C.	49	S. C.	44	J. E.	66
M. C.	45	93	Br. C.	40	B. D.	98	B. M.	68
S. C.	105	105	G. C.	66	D. D.	66	E. N.	94
W. C.	109	109	L. C.	50	P. E.	66	J. R.	47
W. C.	102	107	M. C.	45	R. E.	38		
A. D.	59	112	S. C.	45	E. F.	60		
S. D.	98	123	A. D.	47	G. F.	69		
J. F.	67	90	L. D.	48	J. F.	56		
M. F.	104	104	M. E.	46	K. G.	83		
T. F.	72	102	J. F.	67	B. H.	71		
B. H.	93	93	M. F.	40	S. H.	30		
B. H.	102	102	T. F.	40	A. I.	54		
K. H.	105	105	B. H.	43	F. J.	58		
W. H.	96	112	B. H.	38	J. J.	54		
K. I.	121	121	G. H.	46	J. K.	60		
C. J.	86	111	K. H.	60	M. K.	40		
B. K.	99	99	B. K.	65	B. L.	69		
A. L.	55	62	W. K.	55	C. L.	64		
L. L.	70	77	A. L.	62	L. M.	59		
P. L.	114	114	Al. L.	58	M. M.	44		
T. L.	104	104	L. L.	48	R. N.	51		
J. M.	83	83	P. L.	51	R. N.	53		
M. M.	105	105	T. L.	56	M. P.	46		
R. M.	82	82	B. M.	59	P. R.	54		
J. N.	210	210	J. M.	33	B. S.	76		
J. O.	58	81	M. M.	65	D. S.	49		
R. O.	54	78	J. N.	64	G. S.	72		
J. P.	79	90	J. O.	57	G. S.	33		
L. P.	98	98	R. O.	58	G. T.	64		
D. S.	57	79	J. P.	55	B. W.	61		
P. S.	65	80	D. S.	50	G. W.	67		
S. S.	79	93	P. S.	48	M. W.	63		
G. T.	67	113	S. S.	67	M. W.	67		
W. W.	67	102	G. T.	63	T. W.	67		
Mean	87.2	100.4		53.4		60.5		69.1
SEM	±4.2	±3.5		±1.5		±2.2		±3.8
t	7.33	11.80		0.43		2.50		3.57

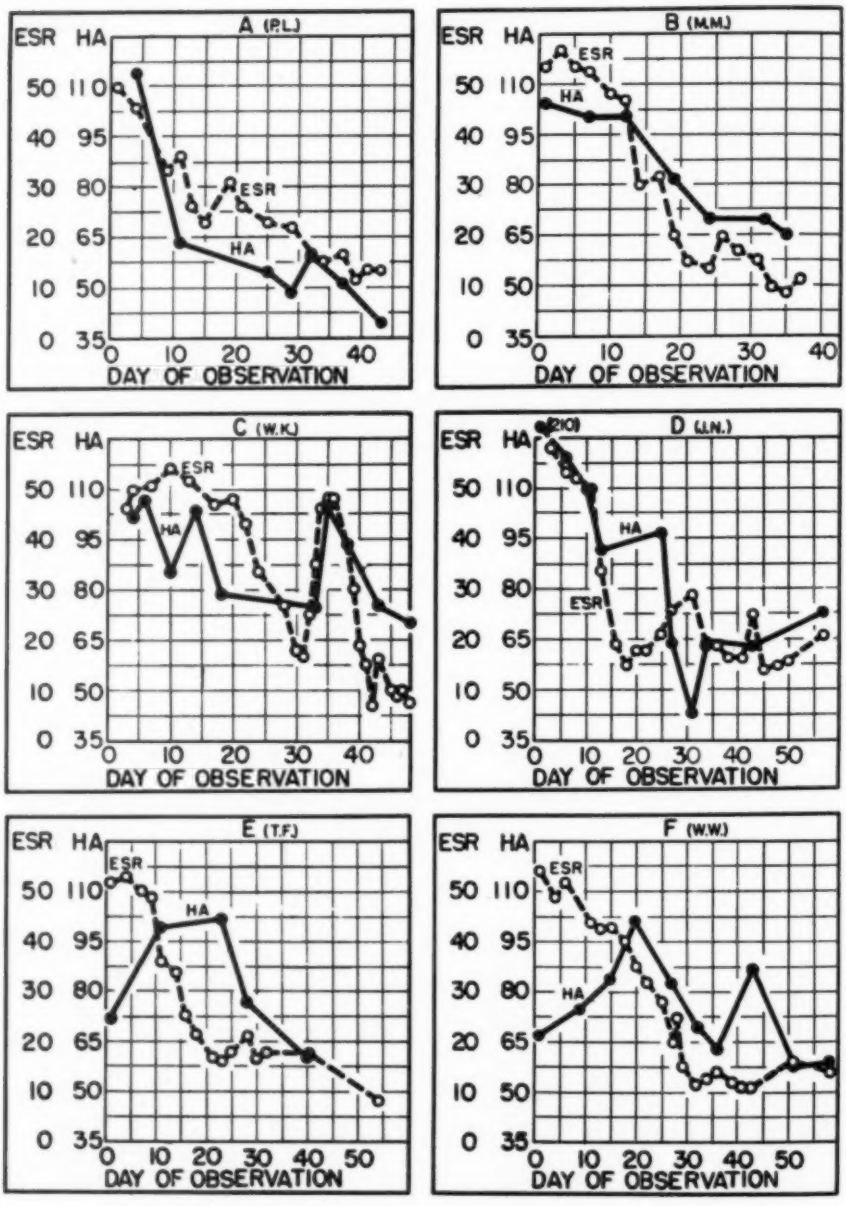

Fig. 1.—Serum hexosamines in patients with acute rheumatic fever.

illness. Fig. 1 shows the results obtained in six illustrative cases comparing in each instance the erythrocyte sedimentation rate with the hexosamine level. As can be seen from the first four cases (A, B, C, D,), there is frequently a strikingly close parallelism exhibited between the curve representing the hexosamine levels and the curve representing the erythrocyte sedimentation rates. On the other hand, as illustrated by graphs E and F, the hexosamine level may be progressively increasing at a time when the patient's erythrocyte sedimentation rate is progressively decreasing. From cases such as these it is obvious that no absolute parallelism exists between these two variables.

TABLE II. SERUM HEXOSAMINE LEVELS IN PATIENTS WITH DISEASES RELATED TO RHEUMATIC FEVER

PT.	INITIAL		MAXIMUM	
	HA	ESR	HA	ESR
Active Juvenile Rheumatoid Arthritis				
R. A.	85	44	102	33
J. C.	66	51	69	53
C. K.	52	30	113	23
J. M.	62	8	65	8
G. S.	65	22	77	20
R. S.	93	19	96	41
G. W.	101	44	101	44
R. W.	82	15	82	15
Acute Glomerulonephritis				
R. A.	81	48	81	48
S. J.	99	43	103	
M. S.	54	42	60	60
Lipoid Nephrosis				
A. H.	72	65	98	55
K. J.	81	44	87	50
V. R.	112	52	112	52
M. W.	101	35	112	50
Anaphylactoid Purpura				
R. F.	90	30	90	30
Periarteritis Nodosa				
B. B.	106	68	116	68

In Table II are shown the results obtained in patients suffering with diseases related to but other than rheumatic fever. The initial hexosamine level and the highest level obtained during the course of the patient's illness with the sedimentation rates obtained at corresponding times are shown for each patient. It will be observed from this table that three of eight patients suffering with active juvenile rheumatoid arthritis and one of three patients suffering with acute glomerulonephritis failed to exhibit abnormally increased serum concentrations of hexosamines at any time during their periods of observation. Because of the small numbers of individuals in each category these data were not submitted to statistical analysis.

DISCUSSION

Although it is not possible to compare directly the data on hexosamines presented here with the data reported by Rosenberg and Schloss[4] or by Boas and Soffer[5] since a different method, which yields lower values, has been employed in this study than was employed by them, certain comparisons of results can be made. Rosenberg and Schloss[4] reported elevations of the serum hexosamine levels upon the initial examination in every one of their twenty-one cases of acute rheumatic fever, whereas in the present study only twenty-seven of forty patients with acute rheumatic fever exhibited such increases. However, at some time during the course of their illnesses all but three of these forty patients exhibited increased serum concentrations of hexosamines. It seems possible that the apparent disparity between the data presented here and those of Rosenberg and Schloss is explicable on the basis of a time differential after onset of illness before the initial samples were obtained. It appears from

the graphic data which they present that their patients were, in general, first studied later in the course of their illnesses than were the patients in the present series. In any event, it would seem obvious that the hexosamine level can be of little value in the diagnosis of acute rheumatic fever, since it is elevated in patients with a great variety of conditions[1-5] and since it is not always elevated in patients with acute rheumatic fever.

Comparison of the data presented here with those of Boas and Soffer[5] on patients with acute disseminated lupus erythematosus reveals that these investigators also found more consistent elevations of hexosamines than were observed in the present study. They found elevated hexosamine levels in seventeen of nineteen patients upon the initial examination. The mean value of the serum hexosamine levels of the individuals they studied was 189 mg. per cent as compared to their values for normal subjects ranging from 85 to 138 mg. per cent with a mean of 107 ± 13.4. The mean value for their patients was 131 per cent of the value representing the extreme upper limit of the normal range. The mean value of the serum hexosamine concentration on the initial determination of patients with acute rheumatic fever in the present series is 85 mg. per cent or 109 per cent of the upper limit of the normal range, and the mean of the maximum hexosamine values obtained in these patients is 100 mg. per cent or 128 per cent of the upper limit of the normal range. Since in the series of Boas and Soffer[5] the initial values also represented the maximum values of hexosamine in most cases, the degree of elevation of the hexosamine level in patients with acute rheumatic fever may be considered to be quite comparable with that in patients with acute disseminated lupus erythematosus. Similar conclusions may be drawn from the data of West and Clark[1] who present the results of analyses for serum hexosamines in seven patients with acute rheumatic fever. In these seven patients the values range from 125 to 184 mg. per cent with a mean value of 159 mg. per cent as compared to their normal range of 76 to 110 mg. per cent.

Rosenberg and Schloss[4] report a definite impression that the greatest elevations of hexosamine levels occurred in the patients who were the most severely ill as judged by the "height and duration of the fever and the intensity of the arthritis or carditis." This impression was essentially substantiated by the results in the present series of cases; however, from the present series the impression was gained that of these criteria of severity of rheumatic fever the severity of arthritis correlated best with the level of serum hexosamines. For example, the patient, J. N., who had the highest serum hexosamine value yet observed in our laboratory, presented with a severe polyarthritis and only slight evidence of carditis. The referral diagnosis in her case, based primarily on her inability to move any part of either lower extremity, was poliomyelitis. Certain other individuals whose presenting symptoms were primarily polyarthritis (K. H., M. M., S. C., W. H., B. H., K. I.) likewise were among those with the highest serum hexosamine levels. On the other hand, certain patients, notably W. C., E. C., S. D., and B. K., had high serum hexosamine levels but had severe carditis as

their principal symptomatology with only moderate arthritis.

In patients other than the severely ill ones, the serum hexosamine level usually becomes elevated above normal limits, but this rise occurs rather slowly. In the present series of patients the serum hexosamine level was elevated above normal limits at the time of the first determination in only two-thirds of the patients; on the other hand, the serum nonglucosamine polysaccharide levels in a similar series of cases were elevated in every case at the time of the initial determination.[6]

The precise significance of elevations of hexosamines in rheumatic fever and related conditions remains obscure. Winzler and co-workers[9] have demonstrated that hexosamines are constituents of serum mucoprotein and are present in the mucoprotein in rather constant concentrations. Kelley and collaborators[10] found that the mucoproteins are elevated in the serum of patients with acute rheumatic fever and a variety of other conditions. However, in view of (a) the demonstration by Winzler and associates[9] of the multiphoretic characteristics of the serum mucoproteins, (b) the absence of knowledge of the fractional distribution of the hexosamine content of the mucoproteins among the various mucoprotein components, (c) the uncertainty that exists as to the occurrence or extent of differential increase in concentration of the various mucoprotein components in the serum in these diseases, and (d) the certainty that hexosamines are associated with fractions of serum protein other than mucoprotein (as determined by standard techniques),[11] it seems unjustified to conclude that the elevation of serum hexosamines is necessarily a reflection of or even causally related to the elevation of serum mucoproteins in patients with rheumatic fever and related conditions.

There is a growing body of evidence that the pathology of rheumatic fever and related diseases consists of a diffuse involvement of tissues of mesenchymal origin.[12-17] Certain evidence would suggest that the demonstrated elevations of serum hexosamine levels in these diseases may represent a reflection of aberrations of hyaluronic acid metabolism. Hyaluronic acid is an important constituent of the amorphous ground substance of the connective tissues of the body, having been found in vitreous humor,[18, 19] in aqueous humor, and Wharton's jelly of the umbilical cord,[19-21] in synovial fluid,[22] and in certain mesenchymal tumors.[23-26] It is a mucopolysaccharide having a molecular weight of 200,000 to 500,000[27] and is a polymer of glucuronic acid and acetyl-N-glucosamine. Hyaluronidase, the enzyme shown by Chain and Duthie[28, 29] to be identical with the "spreading factor" of Duran-Reynals,[30, 31] which is found widely distributed in nature,[21, 22, 32-42] hydrolyzes and depolymerizes hyaluronic acid yielding glucosamine as one of the products. That this action occurs in vivo as well as in vitro is indicated by the demonstration of Schlamowitz and collaborators[43] that the injection of hyaluronidase results in an elevation of the serum hexosamine level.

Meyer[44] has advanced the intriguing speculation that an important role in the pathogenesis of rheumatic fever may be played by injury to the hyaluronic-acid-rich synovial tissues and connective tissues in general by hyaluronidase in or elaborated by the in-

vading streptococcus. Certain observations that would be not inconsistent with this hypothesis have been reported. Group A β-hemolytic streptococci do produce hyaluronidase.[45, 46] Studies of titers of specific antistreptococcus hyaluronidase[47-49] indicate that in association with streptococcus infection, particularly in those individuals who develop rheumatic sequellae, streptococcal hyaluronidase regularly gains entrance to the body. The nonspecific hyaluronidase inhibitor of the serum, studied extensively by Dorfman[50-52] and by Glick[53, 54] although reported by Fulton and associates[55] as being present in the blood serum in normal concentrations in patients with acute rheumatic fever, has since been demonstrated to be present in increased concentrations in these patients' serums.[56-59] Similar elevations have been observed in patients with related diseases.[57, 58, 60]

That hyaluronidase need not necessarily be primarily responsible for the injury to hyaluronic-acid-containing tissues observed in rheumatic fever and related conditions is indicated by the observations of Seifter and coworkers.[61] They found that hyaluronidase causes a markedly increased permeability of synovial membrane. Adrenal cortical extract, adrenocorticotropic hormone, and cortisone antagonize the effect of hyaluronidase on synovial membrane permeability, but the effect of desoxycorticosterone acetate is identical with that of hyaluronidase. They postulate since a nonhyaluronidase spreading factor did not alter the permeability of the membranes, that these changes in permeability may reflect changes in the degree of polymerization of hyaluronic acid with hyaluronidase or desoxycorticosterone acetate causing the reaction to proceed in the direction of depolymerization of hyaluronic acid and the antagonistic hormones causing it to proceed in the direction of its repolymerization. In view of this demonstrated antagonism between hyaluronidase and ACTH or cortisone, the demonstration of increased levels of serum hexosamines following the injection of hyaluronidase,[43] and the demonstration that ACTH causes a decrease to normal levels of the serum hexosamines, initially elevated, in patients with acute disseminated lupus erythematosus, it would appear possible that the elevated hexosamine levels observed in patients with this disease and related diseases, including rheumatic fever, may reflect a deficiency of production or release of adrenal cortical hormones.

SUMMARY

1. Serum hexosamines were determined in 147 patients with rheumatic fever and related diseases.

2. Elevated serum levels of these substances were observed at some time during the illness of all but three of forty patients suffering with acute rheumatic fever but in none of forty patients with convalescent rheumatic fever and in only three of forty patients with inactive rheumatic fever.

3. Only one of ten patients suffering with Sydenham's chorea exhibited an elevated serum level of hexosamines.

4. The serum hexosamine levels were elevated in most but not all patients with other related diseases included in this study.

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TABLES FOR PREDICTING ADULT HEIGHT FROM SKELETAL AGE: REVISED FOR USE WITH THE GREULICH-PYLE HAND STANDARDS

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IN 1946 one of us (N. B.) published in the JOURNAL "Tables for Predicting Adult Height From Present Height and Skeletal Age."[1] These tables were developed for skeletal ages assessed according to the hand standards of T. Wingate Todd.[2] Recently the Todd *Atlas* has been completely revised by Greulich and Pyle.[3] In their revision Greulich and Pyle have changed, somewhat, the criteria for determining normal skeletal age. As a result, readings from the two Atlases are not directly comparable, and predictions of growth from the two sets of standards will not be in perfect agreement. A given skeletal age as determined from the Greulich-Pyle *Atlas* will in most instances represent a different percentage of adult height than the same skeletal age read from the Todd *Atlas*. Put another way, in the two sets of standards a given x-ray will have different skeletal age ratings, even though they represent the same percentage of mature height. Since we may expect the revised Greulich-Pyle *Atlas* to replace the Todd *Atlas* in clinical practice, it has seemed desirable to revise the prediction tables

Our system of prediction is based on the fact that there is a high correlation between the skeletal ages, as read from hand x-rays on this type of standard, and the proportion of their adult stature achieved by children at the time their x-rays were taken. That is, SA (skeletal age) correlates with PMH (per cent of mature height) about .86 at most ages after 9 years, when chronological age is held constant.[4] The new tables have been constructed from data gathered at the University of Californa Institute of Child Welfare, on 192 normal Berkeley children* (103 girls and 89 boys) who were measured and x-rayed every six months (with occasional exceptions) from 8 years through 18 years, or until all epiphyses of the hand were closed. The tables were then validated by applying them to a different group of 46 children† (23 boys and 23 girls).

Each child's height at maturity was taken as 100 per cent, and the fraction of his own mature height was computed for every earlier measuring. The average per cent of mature height (PMH) for a series of ages from one month to 18 years is shown in Fig. 1 and Table I for the Berkeley Growth Study children. The standard deviations from these means (shown by the shaded area in Fig. 1) indicate a wide

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We wish to thank Dr. Jean Walker Macfarlane who has made available for our use x-rays and anthropometric data from the Guidance Study. This material has been used in conjunction with similar data from the Berkeley Growth Study. This investigation was supported (in part) by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

*The subjects of the Guidance Study of the Institute of Child Welfare.

†The Berkeley Growth Study of the Institute of Child Welfare.

spread, among these normal children, in the speeds at which they progress toward their eventual heights. When regrouped according to skeletal age, however, the spread of percentages is greatly reduced during the period of pubescence, as may be seen by the narrowness of the shaded area in the inset curves in Fig. 1. This is one indication of the close relationship between growth in size and the maturation of the skeleton, and demonstrates the usefulness of skeletal age in predicting future growth.

DIRECTIONS FOR TAKING X-RAYS AND MEASURING HEIGHT

In using the tables it is necessary to have a good assessment of skeletal age from an x-ray of the hand, an accurate measurement of height, and a record of the child's age. The following directions are given to facilitate obtaining these data.

TABLE I. MEANS AND STANDARD DEVIATIONS OF PER CENT OF MATURE HEIGHT ACHIEVED AT SUCCESSIVE AGES FROM BIRTH TO 18 YEARS BY THE CHILDREN OF THE BERKELEY GROWTH STUDY

C.A.		BOYS			GIRLS		
		N	MEAN	S.D.	N	MEAN	S.D.
Months	1	17	30.18	.77	20	32.40	1.44
	2	22	32.40	.93	21	34.51	1.56
	3	22	33.93	1.00	23	35.96	1.31
	4	22	35.21	.95	23	37.50	1.08
	5	22	36.50	.99	21	38.78	1.08
	6	22	37.67	.93	21	39.84	1.20
	7	22	38.44	.95	21	40.69	1.20
	8	22	39.22	1.10	23	41.79	1.37
	9	22	40.08	1.07	23	42.20	1.22
	10	22	40.80	1.14	23	43.09	1.37
	11	22	41.53	1.16	21	44.10	1.24
	12	22	42.23	1.04	21	44.67	1.42
	15	22	44.02	1.19	21	46.90	1.18
	18	20	45.64	1.34	19	48.76	1.37
	24	23	48.57	1.44	17	52.15	1.34
	30	23	51.14	1.40	18	54.75	1.22
Years	3.0	23	53.53	1.34	22	57.16	1.20
	4.0	22	57.72	1.38	22	61.84	1.45
	5.0	23	61.60	1.49	23	66.24	1.45
	6.0	23	65.31	1.58	23	70.29	1.60
	7.0	23	69.08	1.60	22	74.28	1.61
	8.0	22	72.40	1.68	23	77.57	1.87
	9.0	22	75.61	1.68	21	81.19	2.00
	9.5	21	77.21	1.66	20	83.03	2.13
	10.0	22	78.40	1.76	23	84.76	2.42
	10.5	23	79.82	1.77	22	86.85	2.71
	11.0	23	81.30	1.94	21	88.65	2.88
	11.5	23	82.54	2.00	21	90.81	3.06
	12.0	20	84.00	2.23	22	92.61	3.27
	12.5	21	85.43	2.49	21	94.72	2.61
	13.0	23	87.32	3.02	18	95.96	2.15
	13.5	21	89.22	3.57	18	97.17	1.70
	14.0	20	91.00	3.96	19	98.27	1.24
	14.5	20	92.60	3.85	19	98.74	.93
	15.0	20	94.60	3.74	21	99.31	.68
	15.5	21	96.00	3.31	21	99.54	.48
	16.0	22	97.09	2.71	21	99.62	.35
	16.5	20	97.95	2.12	20	99.75	.34
	17.0	20	98.79	1.43	22	99.95	.25
	17.5	20	99.28	1.01	19	99.91	.25
	18.0	21	99.55	.58	18	99.96	.11

X-rays are taken of the left hand, which is placed "palm down, hand flat on the film holder, with fingers slightly separated, and the axis of the hand, wrist, and forearm in a straight line. Center the tube half way between the tips of the fingers and distal end of the radius. The radiograph should include the complete fingers and at least 1½ inches of the radius, since all the hand epiphyses as well as those of the distal end of the arm are very important in the skeletal age reading."[5] For children over 6 years of age we have used no-screen cardboard holders. Good results may be obtained with a tube distance of 36 inches, time 1 second, 100 MA, 45-50KV. For use with these tables we recommend reading for SA by the Greulich-Pyle Standards,[3] according to their directions.

Height is measured without shoes, the child "standing tall" against an accurately calibrated solid vertical surface. (A good quality two-meter stick or similar rule calibrated in inches can be firmly affixed beside a vertical board.) Heels and back are touching the wall, the head held in the Frankfort plane (the lower edge of the eye socket and the upper edge of the earhole on a horizontal line). A Baldwin square,[6] which is essentially two boards joined at right angles and held in place by a cross piece, is brought down so that it rests firmly against the measuring scale and comes in firm contact with the top of the head. The height measurement is then read off of the scale at the lower edge of the square.

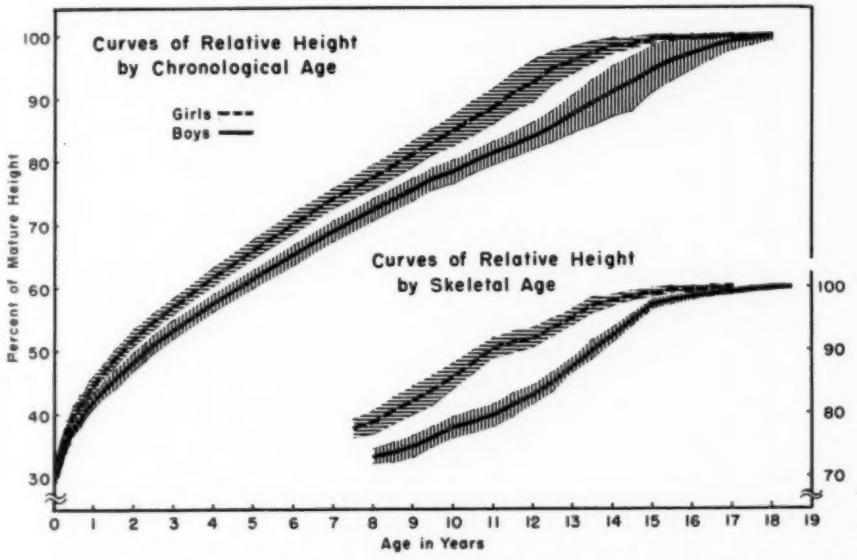

Fig. 1.—Curves of relative height: Mean per cent of mature height, boys and girls separately, by chronological age and by skeletal age. The shaded areas indicate plus and minus one standard deviation, or the middle 68 per cent of a normal distribution.

DIRECTIONS FOR USING THE TABLES

The Greulich-Pyle prediction tables are set up in the same way as the 1946 tables for the Todd standards, with

TABLE IIA. AVERAGE BOYS. PERCENTAGES AND ESTIMATED MATURE HEIGHTS FOR BOYS WITH SKELETAL AGES WITHIN ONE YEAR OF THEIR CHRONOLOGICAL AGES:

SKELETAL AGES 7 THROUGH 12 YEARS

Skeletal Age	**7-0**	7-3	7-6	7-9	**8-0**	8-3	8-6	8-9	**9-0**	9-3	9-6	9-9	**10-0**	10-3	10-6	10-9	**11-0**	11-3	11-6	11-9	12-0	12-3	**12-6**	12-9
% of Mature Height	69.5	70.2	70.9	71.6	72.3	73.1	73.9	74.6	75.2	76.1	76.9	77.7	78.4	79.1	79.5	80.0	80.4	81.2	81.8	82.7	83.4	84.3	85.3	86.3
Ht. (inches)																								
42	60.4																							
43	61.9	61.3	60.6	60.1																				
44	63.3	62.7	62.1	61.5	60.9	60.2																		
45	64.7	64.1	63.5	62.8	62.2	61.6	60.9	60.3																
46	66.2	65.5	64.9	64.2	63.6	62.9	62.2	61.7	61.2	60.4														
47	67.6	67.0	66.3	65.6	65.0	64.3	63.6	63.0	62.5	61.8	61.1	60.5												
48	69.1	68.4	67.7	67.0	66.4	65.7	65.0	64.3	63.8	63.1	62.4	61.8	61.2	60.7	60.4	60.0								
49	70.5	69.8	69.1	68.4	67.8	67.0	66.3	65.7	65.2	64.4	63.7	63.1	62.5	61.9	61.6	61.3	60.9	60.3						
50	71.9	71.2	70.5	69.8	69.2	68.4	67.7	67.0	66.5	65.7	65.0	64.4	63.8	63.2	62.9	62.5	62.2	61.6	61.1	60.5				
51	73.4	72.6	71.9	71.2	**70.5**	69.8	69.0	68.4	67.8	67.0	66.3	65.6	65.1	64.5	64.2	63.8	63.4	62.8	62.3	61.7	61.1	60.5	59.8	
52	74.8	74.1	73.3	72.6	71.9	71.1	70.4	69.7	69.1	68.3	67.6	66.9	66.3	65.7	65.4	65.0	64.7	64.0	63.6	62.9	62.3	61.7	61.0	60.3
53	76.3	75.5	74.8	74.0	73.3	72.5	71.7	71.0	70.5	69.6	68.9	68.2	67.6	67.0	66.7	66.3	65.9	65.3	64.8	64.1	63.5	62.9	62.1	61.4
54	77.7	76.9	76.2	75.4	74.7	73.9	73.1	72.4	71.8	71.0	70.2	69.5	68.9	68.3	67.9	67.5	67.2	66.5	66.0	65.3	64.7	64.1	63.3	62.6
55	79.1	78.3	77.6	76.8	76.1	75.2	74.4	73.7	73.1	72.3	71.5	70.8	70.2	69.5	69.2	68.8	68.4	67.7	67.2	66.5	65.9	65.2	64.5	63.7
56	80.6	79.8	79.0	78.2	77.5	76.6	75.8	75.1	74.5	73.6	72.8	72.1	71.4	70.8	70.4	70.0	69.7	69.0	68.5	67.7	67.1	66.4	65.6	64.9
57			80.4	79.6	78.8	78.0	77.1	76.4	75.8	74.9	74.1	73.4	72.7	72.1	71.7	71.3	70.9	70.2	69.7	68.9	68.3	67.6	66.8	66.0
58					80.2	79.3	78.5	77.7	77.1	76.2	75.4	74.6	74.0	73.3	73.0	72.5	72.1	71.4	70.9	70.1	69.5	68.8	68.0	67.2
59						80.7	79.8	79.1	78.5	77.5	76.7	75.9	75.3	74.6	74.2	73.8	73.4	72.7	72.1	71.3	70.7	70.0	69.2	68.4
60								80.4	79.8	78.8	78.0	77.2	76.5	75.9	75.5	75.0	74.6	73.9	73.3	72.6	71.9	71.2	70.3	69.5
61										80.2	79.3	78.5	77.8	77.1	76.7	76.3	75.9	75.1	74.6	73.8	73.1	72.4	71.5	70.7
62											80.6	79.8	79.1	78.4	78.0	77.5	77.1	76.4	75.8	75.0	74.3	73.5	72.7	71.8
63													80.4	79.6	79.2	78.8	78.4	77.6	77.0	76.2	**75.5**	**74.7**	73.9	73.0
64														80.9	80.5	80.0	79.6	78.8	78.2	77.4	76.7	75.9	75.0	74.2
65																	80.8	80.0	79.5	78.6	77.9	77.1	76.2	75.3
66																			80.7	79.8	79.1	78.3	77.4	76.5
67																					80.3	79.5	78.5	77.6
68																						80.7	79.7	78.8
69																							80.9	80.0

TABLE IIB. AVERAGE BOYS. PERCENTAGES AND ESTIMATED MATURE HEIGHTS FOR BOYS WITH SKELETAL AGES WITHIN ONE YEAR OF THEIR CHRONOLOGICAL AGES:

SKELETAL AGES 13 YEARS TO MATURITY

Skeletal Age	13-0	13-3	13-6	13-9	14-0	14-3	14-6	14-9	15-0	15-3	15-6	15-9	16-0	16-3	16-6	16-9	17-0	17-3	17-6	17-9	18-0	18-3	18-6
% of Mature Height	87.6	89.0	90.2	91.4	92.7	93.8	94.8	95.8	96.8	97.3	97.6	98.0	98.2	98.5	98.7	98.9	99.1	99.3	99.4	99.5	99.6	99.8	100.0
Ht. (inches)																							
53	60.5																						
54	61.6	60.7																					
55	62.8	61.8	61.0	60.2																			
56	63.9	62.9	62.1	61.3	60.4																		
57	65.1	64.0	63.2	62.4	61.5	60.8	60.1																
58	66.2	65.2	64.3	63.5	62.6	61.8	61.2	60.5															
59	67.4	66.3	65.4	64.6	63.6	62.9	62.2	61.6	61.0	60.6	60.5	60.2	60.1										
60	68.5	67.4	66.5	65.6	64.7	64.0	63.3	62.6	62.0	61.7	61.5	61.2	61.1	60.9	60.8	60.7	60.5	60.4	60.4	60.3	60.2	60.1	60.0
61	69.6	68.5	67.6	66.7	65.8	65.0	64.3	63.7	63.0	62.7	62.5	62.2	62.1	61.9	61.8	61.7	61.6	61.4	61.4	61.3	61.2	61.1	61.0
62	70.8	69.7	68.7	67.8	66.9	66.1	65.4	64.7	64.1	63.7	63.5	63.3	63.1	62.9	62.8	62.7	62.6	62.4	62.4	62.3	62.2	62.1	62.0
63	71.9	70.8	69.8	68.9	68.0	67.2	66.5	65.8	65.1	64.7	64.5	64.3	64.2	64.0	63.8	63.7	63.6	63.4	63.4	63.3	63.3	63.1	63.0
64	73.1	71.9	71.0	70.0	69.0	68.2	67.5	66.8	66.1	65.8	65.6	65.3	65.2	65.0	64.8	64.7	64.6	64.4	64.4	64.3	64.3	64.1	64.0
65	74.2	73.0	72.1	71.1	70.1	69.3	68.6	67.8	67.2	66.8	66.6	66.3	66.2	66.0	65.9	65.7	65.6	65.5	65.4	65.3	65.3	65.1	65.0
66	75.3	74.2	73.2	72.2	71.2	70.4	69.6	68.9	68.2	67.8	67.6	67.3	67.2	67.0	66.9	66.7	66.6	66.5	66.4	66.3	66.3	66.1	66.0
67	76.5	75.3	74.3	73.3	72.3	71.4	70.7	69.9	69.2	68.9	68.6	68.4	68.2	68.0	67.9	67.7	67.6	67.5	67.4	67.3	67.3	67.1	67.0
68	77.6	76.4	75.4	74.4	73.4	72.5	71.7	71.0	70.3	69.9	69.7	69.4	69.2	69.0	68.9	68.8	68.6	68.5	68.4	68.3	68.3	68.1	68.0
69	78.8	77.5	76.5	75.5	74.4	73.6	72.8	72.0	71.3	70.9	70.7	70.4	70.3	70.0	69.9	69.8	69.6	69.5	69.4	69.3	69.3	69.1	69.0
70	79.9	78.7	77.6	76.6	75.5	74.6	73.8	73.1	72.3	71.9	71.7	71.4	71.3	71.1	70.9	70.8	70.6	70.5	70.4	70.4	70.3	70.1	70.0
71		79.8	78.7	77.7	76.6	75.7	74.9	74.1	73.4	73.0	72.7	72.4	72.3	72.1	71.9	71.8	71.6	71.5	71.4	71.4	71.3	71.1	71.0
72		80.9	79.8	78.8	77.7	76.8	75.9	75.2	74.4	74.0	73.8	73.5	73.3	73.1	73.0	72.8	72.7	72.5	72.4	72.4	72.3	72.1	72.0
73			80.9	79.9	78.7	77.8	77.0	76.2	75.4	75.0	74.8	74.5	74.3	74.1	74.0	73.8	73.7	73.5	73.4	73.4	73.3	73.1	73.0
74					79.8	78.9	78.1	77.2	76.4	76.0	75.8	75.5	75.4	75.1	75.0	74.8	74.7	74.5	74.4	74.4	74.3	74.1	74.0
75					80.9	80.0	79.1	78.3	77.5	77.1	76.8	76.5	76.4	76.1	76.0	75.8	75.7	75.5	75.5	75.4	75.3	75.2	75.0
76							80.2	79.3	78.5	78.1	77.9	77.6	77.4	77.2	77.0	76.8	76.7	76.5	76.5	76.4	76.3	76.2	76.0
77								80.4	79.5	79.1	78.9	78.6	78.4	78.2	78.0	77.9	77.7	77.5	77.5	77.4	77.3	77.2	77.0
78									80.6	80.2	79.9	79.6	79.4	79.2	79.0	78.9	78.7	78.5	78.5	78.4	78.3	78.2	78.0

TABLE IIC. ACCELERATED BOYS. PERCENTAGES AND ESTIMATED MATURE HEIGHTS FOR BOYS WITH SKELETAL AGES ONE YEAR OR MORE ADVANCED OVER THEIR CHRONOLOGICAL AGES:

SKELETAL AGES 7 THROUGH 11 YEARS

Skeletal Age	7-0	7-3	7-6	7-9	8-0	8-3	8-6	8-9	9-0	9-3	9-6	9-9	10-0	10-3	10-6	10-9	11-0	11-3	11-6	11-9
% of Mature Height	67.0	67.6	68.3	68.9	69.6	70.3	70.9	71.5	72.0	72.8	73.4	74.1	74.7	75.3	75.8	76.3	76.7	77.6	78.6	80.0
Ht. (inches)																				
41	61.2	60.7	60.0																	
42	62.7	62.1	61.5	61.0	60.3															
43	64.2	63.6	63.0	62.4	61.8	61.2	60.6	60.1												
44	65.7	65.1	64.4	63.9	63.2	62.6	62.1	61.5	61.1	60.4										
45	67.2	66.6	65.9	65.3	64.7	64.0	63.5	62.9	62.5	61.8	61.3	60.7	60.2							
46	68.7	68.0	67.3	66.8	66.1	65.4	64.9	64.3	63.9	63.2	62.7	62.1	61.6	61.1	60.7	60.3	60.0			
47	70.1	69.5	68.8	68.2	67.5	66.9	66.3	65.7	65.3	64.6	64.0	63.4	62.9	62.4	62.0	61.6	61.3	60.6		
48	71.6	71.0	70.3	69.7	69.0	68.3	67.7	67.1	66.7	65.9	65.4	64.8	64.3	63.7	63.3	62.9	62.6	61.9	61.1	60.0
49	73.1	72.5	71.7	71.1	70.4	69.7	69.1	68.5	68.1	67.3	66.8	66.1	65.6	65.1	64.6	64.2	63.9	63.1	62.3	61.3
50	74.6	74.0	73.2	72.6	71.8	71.1	70.5	69.9	69.4	68.7	68.1	67.5	66.9	66.4	66.0	65.5	65.2	64.4	63.6	62.5
51	76.2	75.4	74.7	74.0	73.3	72.5	71.9	71.3	70.8	70.1	69.5	68.8	68.3	67.7	67.3	66.8	66.5	65.7	64.9	63.8
52	77.6	76.9	76.1	75.5	74.7	74.0	73.3	72.7	72.2	71.4	70.8	70.2	69.6	69.1	68.6	68.2	67.8	67.0	66.2	65.0
53	79.1	78.4	77.6	76.9	76.2	75.4	74.8	74.1	73.6	72.8	72.2	71.5	71.0	70.4	69.9	69.5	69.1	68.3	67.4	66.3
54	80.6	79.9	79.1	78.4	77.6	76.8	76.2	75.5	75.0	74.2	73.6	72.9	72.3	71.7	71.2	70.8	70.4	69.6	68.7	67.5
55			80.5	79.8	79.0	78.2	77.6	76.9	76.4	75.5	74.9	74.2	73.6	73.0	72.6	72.1	71.7	70.9	70.0	68.8
56					80.5	79.7	79.0	78.3	77.8	76.9	76.3	75.6	75.0	74.4	73.9	73.4	73.0	72.2	71.2	70.0
57							80.4	79.7	79.2	78.3	77.7	76.9	76.3	75.7	75.2	74.7	74.3	73.5	72.5	71.3
58									80.6	79.7	79.0	78.3	77.6	77.0	76.5	76.0	75.6	74.7	73.8	72.5
59											80.4	79.6	79.0	78.4	77.8	77.3	76.9	76.0	75.1	73.8
60													80.3	79.7	79.2	78.6	78.2	77.3	76.3	75.0
61															80.5	79.9	79.5	78.6	77.6	76.3
62																81.3	80.8	79.9	78.9	77.5
63																			80.2	78.8
64																				80.0

TABLE IID. ACCELERATED BOYS. PERCENTAGES AND ESTIMATED MATURE HEIGHTS FOR BOYS WITH SKELETAL AGES ONE YEAR OR MORE ADVANCED OVER THEIR CHRONOLOGICAL AGES:

SKELETAL AGES 12 THROUGH 17 YEARS

Skeletal Age	12-0	12-3	**12-6**	12-9	13-0	**13-3**	13-6	13-9	**14-0**	14-3	14-6	14-9	**15-0**	15-3	**15-6**	15-9	**16-0**	16-3	16-6	16-9	**17-0**
% of Mature Height	80.9	81.8	82.8	83.9	85.0	86.3	87.5	89.0	90.5	91.8	93.0	94.3	95.8	96.7	97.1	97.6	98.0	98.3	98.5	98.8	99.0
Ht. (inches)																					
49	60.6																				
50	61.8	61.1	60.4																		
51	63.0	62.3	61.6	60.8	60.0																
52	64.3	63.6	62.8	62.0	61.2	60.3															
53	65.5	64.8	64.0	63.2	62.4	61.4	60.6														
54	66.7	66.0	65.2	64.4	63.5	62.6	61.7	60.7													
55	68.0	67.2	66.4	65.6	64.7	63.7	62.9	61.8	60.8												
56	69.2	68.5	67.6	66.7	65.9	64.9	64.0	62.9	61.9	61.0	60.2										
57	70.5	69.7	68.8	67.9	67.1	66.0	65.1	64.0	63.0	62.1	61.3	60.4									
58	71.7	70.9	70.0	69.1	68.2	67.2	66.3	65.2	64.1	63.2	62.4	61.5	60.5	60.0							
59	72.9	72.1	71.3	70.3	69.4	68.4	67.4	66.3	65.2	64.3	63.4	62.6	61.6	61.0	60.8						
60	74.2	73.4	72.5	71.5	70.6	69.5	68.6	67.4	66.3	65.4	64.5	63.6	62.6	62.0	61.8	60.5	60.2	60.0			
61	75.4	74.6	73.7	72.7	71.8	70.7	69.7	68.5	67.4	66.4	65.6	64.7	63.7	63.1	62.8	61.5	61.2	61.0	60.9	60.7	60.6
62	76.6	75.8	74.9	73.9	72.9	71.8	70.9	69.7	68.5	67.5	66.7	65.7	64.7	64.1	63.9	62.5	62.2	62.1	61.9	61.7	61.6
63	77.9	77.0	76.1	75.1	74.1	73.0	72.0	70.8	69.6	68.6	67.7	66.8	65.8	65.1	64.9	63.5	63.3	63.1	62.9	62.8	62.6
64	79.1	78.2	77.3	76.3	75.3	74.2	73.1	71.9	70.7	69.7	68.8	67.9	66.8	66.2	65.9	64.5	64.3	64.1	64.0	63.8	63.6
65	80.3	79.5	78.5	77.5	76.5	75.3	74.3	73.0	71.8	70.8	69.9	68.9	67.8	67.2	66.9	65.6	65.3	65.1	65.0	64.8	64.6
66		80.7	79.7	78.7	77.6	76.5	75.4	74.2	72.9	71.9	71.0	70.0	68.9	68.3	68.0	66.6	66.3	66.1	66.0	65.8	65.7
67			80.9	79.9	78.8	77.6	76.6	75.3	74.0	73.0	72.0	71.1	69.9	69.3	69.0	67.6	67.3	67.1	67.0	66.8	66.7
68					80.0	78.8	77.7	76.4	75.1	74.1	73.1	72.1	71.0	70.3	70.0	68.6	68.4	68.2	68.0	67.8	67.7
69						80.0	78.9	77.5	76.2	75.2	74.2	73.2	72.0	71.4	71.1	69.7	69.4	69.2	69.0	68.8	68.7
70							80.0	78.7	77.3	76.3	75.3	74.2	73.1	72.4	72.1	70.7	70.4	70.2	70.0	69.8	69.7
71								79.8	78.5	77.3	76.3	75.3	74.1	73.4	73.1	71.7	71.4	71.2	71.1	70.8	70.7
72								80.9	79.6	78.4	77.4	76.4	75.2	74.5	74.2	72.7	72.4	72.2	72.1	71.9	71.7
73									80.7	79.5	78.5	77.4	76.2	75.5	75.2	73.8	73.5	73.2	73.1	72.9	72.7
74										80.6	79.6	78.5	77.2	76.5	76.2	74.8	74.5	74.3	74.1	73.9	73.7
75											80.6	79.5	78.3	77.6	77.2	75.8	75.5	75.3	75.1	74.9	74.7
76												80.6	79.3	78.6	78.3	76.8	76.5	76.3	76.1	75.9	75.8
77													80.4	79.6	79.3	77.9	77.6	77.3	77.2	76.9	76.8
78														80.7	80.3	78.9	78.6	78.3	78.2	77.9	77.8
																79.9	79.6	79.3	79.2	78.9	78.8

TABLE IIE. RETARDED BOYS. PERCENTAGES AND ESTIMATED MATURE HEIGHTS FOR BOYS WITH SKELETAL AGES ONE YEAR OR MORE RETARDED FOR THEIR CHRONOLOGICAL AGES:

SKELETAL AGES 6 THROUGH 13 YEARS

Skeletal Age	**6-0**	6-3	6-6	6-9	**7-0**	7-3	7-6	7-9	**8-0**	8-3	8-6	8-9	**9-0**	9-3	9-6	9-9	**10-0**	10-3	10-6	10-9	**11-0**	11-3	11-6	11-9	12-0	12-3	**12-6**	12-9	13-0
% of Mature Height	68.0	69.0	70.0	70.9	71.8	72.8	73.8	74.7	75.6	76.5	77.3	77.9	78.6	79.4	80.0	80.7	81.2	81.6	81.9	82.1	82.3	82.7	83.2	83.9	84.5	85.2	86.0	86.9	88.0
Ht. (inches)																													
41	60.3																												
42	61.8	60.9	60.0																										
43	63.2	62.3	61.4	60.6																									
44	64.7	63.8	62.9	62.1	61.3	60.4																							
45	66.2	65.2	64.3	63.5	62.7	61.8	61.0	60.2																					
46	67.6	66.7	65.7	64.9	64.1	63.2	62.3	61.6	60.8	60.1																			
47	69.1	68.1	67.1	66.3	65.5	64.6	63.7	62.9	62.2	61.4	60.8	60.3																	
48	70.6	69.6	68.6	67.7	66.9	65.9	65.0	64.3	63.5	62.7	62.1	61.6	61.1	60.5	60.0														
49	72.1	71.0	70.0	69.1	68.3	67.3	66.4	65.6	64.8	64.1	63.4	62.9	62.3	61.7	61.3	60.7	60.3	60.0											
50	73.5	72.5	71.4	70.5	69.6	68.7	67.8	66.9	66.1	65.4	64.7	64.2	63.6	63.0	62.5	62.0	61.6	61.3	61.1	60.9	60.8	60.5	60.1						
51	75.0	73.9	72.9	71.9	71.0	70.1	69.1	68.3	67.5	66.7	66.0	65.5	64.9	64.2	63.8	63.2	62.8	62.5	62.3	62.1	62.0	61.7	61.3	60.8	60.4				
52	76.5	75.4	74.3	73.3	72.4	71.4	70.5	69.6	68.8	68.0	67.3	66.8	66.2	65.5	65.0	64.4	64.0	63.7	63.5	63.3	63.2	62.9	62.5	62.0	61.5	61.0	60.5		
53	77.9	76.8	75.7	74.8	73.8	72.8	71.8	71.0	70.1	69.3	68.6	68.0	67.4	66.8	66.3	65.7	65.3	65.0	64.7	64.6	64.4	64.1	63.7	63.2	62.7	62.2	61.6	61.0	60.2
54	79.4	78.3	77.1	76.2	75.2	74.2	73.2	72.3	71.4	70.6	69.9	69.3	68.7	68.0	67.5	66.9	66.5	66.2	65.9	65.8	65.6	65.3	64.9	64.4	63.9	63.4	62.8	62.1	61.4
55	80.9	79.7	78.6	77.6	76.6	75.5	74.5	73.6	72.8	71.9	71.2	70.6	70.0	69.3	68.8	68.2	67.7	67.4	67.2	67.0	66.8	66.5	66.1	65.6	65.1	64.6	64.0	63.3	62.5
56			80.0	79.0	78.0	76.9	75.9	75.0	74.1	73.2	72.4	71.9	71.2	70.5	70.0	69.4	69.0	68.6	68.4	68.2	68.0	67.7	67.3	66.7	66.3	65.7	65.1	64.4	63.6
57				80.4	79.4	78.3	77.2	76.3	75.4	74.5	73.7	73.2	72.5	71.8	71.3	70.6	70.2	69.9	69.6	69.4	69.3	68.9	68.5	67.9	67.5	66.9	66.3	65.6	64.8
58					80.8	79.7	78.6	77.6	76.7	75.8	75.0	74.5	73.8	73.0	72.5	71.9	71.4	71.1	70.8	70.6	70.5	70.1	69.7	69.1	68.6	68.1	67.4	66.7	65.9
59							79.9	79.0	78.0	77.1	76.3	75.7	75.1	74.3	73.8	73.1	72.7	72.3	72.0	71.9	71.7	71.3	70.9	70.3	69.8	69.2	68.6	67.9	67.0
60								80.3	79.4	78.4	77.6	77.0	76.3	75.6	75.0	74.4	73.9	73.5	73.3	73.1	72.9	72.6	72.1	71.5	71.0	70.4	69.8	69.0	68.2
61									80.7	79.7	78.9	78.3	77.6	76.8	76.3	75.6	75.1	74.8	74.5	74.3	74.1	73.8	73.3	72.7	72.2	71.6	70.9	70.2	69.3
62											80.2	79.6	78.9	78.1	77.5	76.8	76.4	76.0	75.7	75.5	75.3	75.0	74.5	73.9	73.4	72.8	72.1	71.3	70.5
63												80.9	80.2	79.3	78.8	78.1	77.6	77.2	76.9	76.7	76.5	76.2	75.7	75.1	74.6	73.9	73.3	72.5	71.6
64														80.6	80.0	79.3	78.8	78.4	78.1	78.0	77.8	77.4	76.9	76.3	75.7	75.1	74.4	73.6	72.7
65																80.5	80.0	79.7	79.4	79.2	79.0	78.6	78.1	77.5	76.9	76.3	75.6	74.8	73.9
66																		80.9	80.6	80.4	80.2	79.8	79.3	78.7	78.1	77.5	76.7	75.9	75.(
67																					80.5	79.9	79.3	78.6	77.9	77.1	76.1		

supplementary tables for retarded and accelerated children at the younger ages. In each table the skeletal ages, by three-month intervals, are given across the top, with the corresponding PMH directly under its SA. Mature heights may be computed from these percentages, by dividing the child's height by the percentage which corresponds to his SA. Or predicted height may be read off directly from the tables. It is important, for reliable prediction from the tables, to use the correct table for the child's sex (Tables II for boys and Tables III for girls), and to select the table suitable for his rate of maturing. When within one year of a child's chronological age, use Tables IIA or IIB for boys, IIIA or IIIB for girls; when accelerated a year or more, use Tables IIC and IID or IIIC and IIID; and when retarded a year or more, use Tables IIE or IIIE and IIIF.

The most frequent mature heights have been computed for SA intervals of three months and height intervals of one inch. These predictions are given in the body of the tables. For example: A 13-year-old boy with an SA of 13 years 3 months is 60 inches tall. From Table IIB we find 60 inches in the left-hand column and follow across this row to the SA column of 13-3. The figure at this intersection, 67.4 inches, is the predicted mature height for this boy. If the measures or SA's do not fall exactly at the one-inch or three-month intervals, or are outside the range of prediction given in the table, we may interpolate, or make direct computations. For example, if the 13-year-old boy is only 51.5 inches tall, his mature height may be computed by dividing his present height by 89.0, which is the PMH for SA 13-3. This will predict an eventual height (or 100 per cent) of 57.9 inches.

Another boy may be 14 years old, 67½ inches tall, and have an SA of 15½ years. From TableIID we would predict a mature height from the 15-6 SA column at a point half way between 69 and 70 inches, or 69½ inches.

To take another example: A girl who is 12 years old has an SA of 10 years 3 months, and is 55 inches tall. Using Table IIIE, the intersection of the 10-3 column and the 55 inch row gives a probable mature height of 62.2 inches.

Predictions for ages younger than those given in the tables are subject to large errors. But it is sometimes desirable to make some prediction at an early age. Adult heights could then be estimated from the percentages given in Table I.

INTERPRETATION

The predictions from the tables are not perfectly accurate, even though after 9 years of age they are far better than estimates made on the basis of age without regard to maturational status.[1] There are several sources of error which must be kept in mind when making any predictions.

(a) X-rays may be inaccurately read. Accuracy can be increased by practice in the use of the standards, but such assessments always remain approximations. It is, therefore, very desirable to reduce the error by making several independent readings (by the same or different persons) and then to take the average of these readings.

(b) These prediction tables were developed from the Greulich-Pyle stand-

TABLE IIIA. AVERAGE GIRLS. PERCENTAGES AND ESTIMATED MATURE HEIGHTS FOR GIRLS WITH SKELETAL AGES WITHIN ONE YEAR OF THEIR CHRONOLOGICAL AGES:

SKELETAL AGES 6 THROUGH 11 YEARS

Skeletal Age	6-0	6-3	6-6	**6-10**	7-0	7-3	7-6	**7-10**	8-0	8-3	8-6	**8-10**	9-0	9-3	9-6	9-9	**10-0**	10-3	10-6	10-9	**11-0**	11-3	11-6	11-9
% of Mature Height	72.0	72.9	73.8	75.1	75.7	76.5	77.2	78.2	79.0	80.1	81.0	82.1	82.7	83.6	84.4	85.3	86.2	87.4	88.4	89.6	90.6	91.0	91.4	91.8
Ht. (inches)																								
37	51.4																							
38	52.8	52.1	51.5																					
39	54.2	53.5	52.8	52.0	51.5	51.0																		
40	55.6	54.9	54.2	53.3	52.8	52.3	51.8	51.2																
41	56.9	56.2	55.6	54.6	54.2	53.6	53.1	52.4	51.9	51.2														
42	58.3	57.6	56.9	55.9	55.5	54.9	54.4	53.7	53.2	52.4	51.9	51.2												
43	59.7	59.0	58.3	57.3	56.8	56.2	55.7	55.0	54.4	53.7	53.1	52.4	52.0	51.4										
44	61.1	60.4	59.6	58.6	58.1	57.5	57.0	56.3	55.7	54.9	54.3	53.6	53.2	52.6	52.1	51.6	51.0							
45	62.5	61.7	61.0	59.9	59.4	58.8	58.3	57.5	57.0	56.2	55.6	54.8	54.4	53.8	53.3	52.8	52.2	51.5						
46	63.9	63.1	62.3	61.3	60.8	60.1	59.6	58.8	58.2	57.4	56.8	56.0	55.6	55.0	54.5	53.9	53.4	52.6	52.0	51.3				
47	65.3	64.5	63.7	62.6	62.1	61.4	60.9	60.1	59.5	58.7	58.0	57.2	56.8	56.2	55.7	55.1	54.5	53.8	53.2	52.5	51.9	51.6	51.4	51.2
48	66.7	65.8	65.0	63.9	63.4	62.7	62.2	61.4	60.8	59.9	59.3	58.5	58.0	57.4	56.9	56.3	55.7	54.9	54.3	53.6	53.0	52.7	52.5	52.3
49	68.1	67.2	66.4	65.2	64.7	64.1	63.5	62.7	62.0	61.2	60.5	59.7	59.3	58.6	58.1	57.4	56.8	56.1	55.4	54.7	54.1	53.8	53.6	53.4
50	69.4	68.6	67.8	66.6	66.1	65.4	64.8	63.9	63.3	62.4	61.7	60.9	60.5	59.8	59.2	58.6	58.0	57.2	56.6	55.8	55.2	54.9	54.7	54.5
51	70.8	70.0	69.1	67.9	67.4	66.7	66.1	65.2	64.6	63.7	63.0	62.1	61.7	61.0	60.4	59.8	59.2	58.4	57.7	56.9	56.3	56.0	55.8	55.6
52	72.2	71.3	70.5	69.2	68.7	68.0	67.4	66.5	65.8	64.9	64.2	63.3	62.9	62.2	61.6	61.0	60.3	59.5	58.8	58.0	57.4	57.1	56.9	56.6
53	73.6	72.7	71.8	70.6	70.0	69.3	68.7	67.8	67.1	66.2	65.4	64.6	64.1	63.4	62.8	62.1	61.5	60.6	60.0	59.2	58.5	58.2	58.0	57.7
54		74.1	73.2	71.9	71.3	70.6	69.9	69.1	68.4	67.4	66.7	65.8	65.3	64.6	64.0	63.3	62.6	61.8	61.1	60.3	59.6	59.3	59.1	58.8
55			74.5	73.2	72.7	71.9	71.2	70.3	69.6	68.7	67.9	67.0	66.5	65.8	65.2	64.5	63.8	62.9	62.2	61.4	60.7	60.4	60.2	59.9
56				74.6	74.0	73.2	72.5	71.6	70.9	69.9	69.1	68.2	67.7	67.0	66.4	65.7	65.0	64.1	63.3	62.5	61.8	61.5	61.3	61.0
57						74.5	73.8	72.9	72.2	71.2	70.4	69.4	68.9	68.2	67.5	66.8	66.1	65.2	64.5	63.6	62.9	62.6	62.4	62.1
58								74.2	73.4	72.4	71.6	70.6	70.1	69.4	68.7	68.0	67.3	66.4	65.6	64.7	64.0	63.7	63.5	63.2
59									74.7	73.7	72.8	71.9	71.3	70.6	69.9	69.2	68.4	67.5	66.7	65.8	65.1	64.8	64.6	64.3
60										74.9	74.1	73.1	72.6	71.8	71.1	70.3	69.6	68.7	67.9	67.0	66.2	65.9	65.6	65.4
61												74.3	73.8	73.0	72.3	71.5	70.8	69.8	69.0	68.1	67.3	67.0	66.7	66.4
62														74.2	73.5	72.7	71.9	70.9	70.1	69.2	68.4	68.1	67.8	67.5
63															74.6	73.9	73.1	72.1	71.3	70.3	69.5	69.2	68.9	68.6
64																	74.2	73.2	72.4	71.4	70.6	70.3	70.0	69.7
65																		74.4	73.5	72.5	71.7	71.4	71.1	70.8
66																			74.7	73.7	72.9	72.5	72.2	71.9
67																				74.8	74.0	73.6	73.3	73.0
68																						74.7	74.4	74.1

TABLE IIIB. AVERAGE GIRLS. PERCENTAGES AND ESTIMATED MATURE HEIGHTS FOR GIRLS WITH SKELETAL AGES WITHIN ONE YEAR OF THEIR CHRONOLOGICAL AGES:

SKELETAL AGES 12 THROUGH 18 YEARS

Skeletal Age	12-0	12-3	12-6	12-9	13-0	13-3	13-6	13-9	14-0	14-3	14-6	14-9	15-0	15-3	15-6	15-9	16-0	16-3	16-6	16-9	17-0	17-6	18-0
% of Mature Height	92.2	93.2	94.1	95.0	95.8	96.7	97.4	97.8	98.0	98.3	98.6	98.8	99.0	99.1	99.3	99.4	99.6	99.6	99.7	99.8	99.9	99.95	100.0
Ht. (inches)																							
47	51.0																						
48	52.1	51.5	51.0																				
49	53.1	52.6	52.1	51.6	51.1																		
50	54.2	53.6	53.1	52.6	52.2	51.7	51.3	51.1	51.0														
51	55.3	54.7	54.2	53.7	53.2	52.7	52.4	52.1	52.0	51.9	51.7	51.6	51.5	51.5	51.4	51.3	51.2	51.2	51.2	51.1	51.1	51.0	51.0
52	56.4	55.8	55.3	54.7	54.3	53.8	53.4	53.2	53.1	52.9	52.7	52.6	52.5	52.5	52.4	52.3	52.2	52.2	52.2	52.1	52.1	52.0	52.0
53	57.5	56.9	56.3	55.8	55.3	54.8	54.4	54.2	54.1	53.9	53.8	53.6	53.5	53.5	53.4	53.3	53.2	53.2	53.2	53.1	53.1	53.0	53.0
54	58.6	57.9	57.4	56.8	56.4	55.8	55.4	55.2	55.1	54.9	54.8	54.7	54.5	54.5	54.4	54.3	54.2	54.2	54.2	54.1	54.1	54.0	54.0
55	59.7	59.0	58.4	57.9	57.4	56.9	56.5	56.2	56.1	56.0	55.8	55.7	55.6	55.5	55.4	55.3	55.2	55.2	55.2	55.1	55.1	55.0	55.0
56	60.7	60.1	59.5	58.9	58.5	57.9	57.5	57.3	57.1	57.0	56.8	56.7	56.6	56.5	56.4	56.3	56.2	56.2	56.2	56.1	56.1	56.0	56.0
57	61.8	61.2	60.6	60.0	59.5	58.9	58.5	58.3	58.2	58.0	57.8	57.7	57.6	57.5	57.4	57.3	57.2	57.2	57.2	57.1	57.1	57.0	57.0
58	62.9	62.2	61.6	61.1	60.5	60.0	59.5	59.3	59.2	59.0	58.8	58.7	58.6	58.5	58.4	58.3	58.2	58.2	58.2	58.1	58.1	58.0	58.0
59	64.0	63.3	62.7	62.1	61.6	61.0	60.6	60.3	60.2	60.0	59.8	59.7	59.6	59.5	59.4	59.4	59.2	59.2	59.2	59.1	59.1	59.0	59.0
60	65.1	64.4	63.8	63.2	62.6	62.0	61.6	61.3	61.2	61.0	60.9	60.7	60.6	60.5	60.4	60.4	60.2	60.2	60.2	60.1	60.1	60.0	60.0
61	66.2	65.5	64.8	64.2	63.7	63.1	62.6	62.4	62.2	62.1	61.9	61.7	61.6	61.6	61.4	61.4	61.2	61.2	61.2	61.1	61.1	61.0	61.0
62	67.2	66.5	65.9	65.3	64.7	64.1	63.7	63.4	63.3	63.1	62.9	62.8	62.6	62.6	62.4	62.4	62.2	62.2	62.2	62.1	62.1	62.0	62.0
63	68.3	67.6	67.0	66.3	65.8	65.1	64.7	64.4	64.3	64.1	63.9	63.8	63.6	63.6	63.4	63.4	63.3	63.3	63.2	63.1	63.1	63.0	63.0
64	69.4	68.7	68.0	67.4	66.8	66.2	65.7	65.4	65.3	65.1	64.9	64.8	64.6	64.6	64.4	64.4	64.3	64.3	64.2	64.1	64.1	64.0	64.0
65	70.5	69.7	69.1	68.4	67.8	67.2	66.7	66.5	66.3	66.1	65.9	65.8	65.7	65.6	65.5	65.4	65.3	65.3	65.2	65.1	65.1	65.0	65.0
66	71.6	70.8	70.1	69.5	68.9	68.3	67.8	67.5	67.3	67.1	66.9	66.8	66.7	66.6	66.5	66.4	66.3	66.3	66.2	66.1	66.1	66.0	66.0
67	72.7	71.9	71.2	70.5	69.9	69.3	68.8	68.5	68.4	68.2	68.0	67.8	67.7	67.6	67.5	67.4	67.3	67.3	67.2	67.1	67.1	67.0	67.0
68	73.8	73.0	72.3	71.6	71.0	70.3	69.8	69.5	69.4	69.2	69.0	68.8	68.7	68.6	68.5	68.4	68.3	68.3	68.2	68.1	68.1	68.0	68.0
69	74.8	74.0	73.3	72.6	72.0	71.4	70.8	70.6	70.4	70.2	70.0	69.8	69.7	69.6	69.5	69.4	69.3	69.3	69.2	69.1	69.1	69.0	69.0
70			74.4	73.7	73.1	72.4	71.9	71.6	71.4	71.2	71.0	70.8	70.7	70.6	70.5	70.4	70.3	70.3	70.2	70.1	70.1	70.0	70.0
71				74.7	74.1	73.4	72.9	72.6	72.4	72.2	72.0	71.9	71.7	71.6	71.5	71.4	71.3	71.3	71.2	71.1	71.1	71.0	71.0
72						74.5	73.9	73.6	73.5	73.2	73.0	72.9	72.7	72.7	72.5	72.4	72.3	72.3	72.2	72.1	72.1	72.0	72.0
73							74.9	74.6	74.5	74.3	74.0	73.9	73.7	73.7	73.5	73.4	73.3	73.3	73.2	73.1	73.1	73.0	73.0
74												74.9	74.7	74.7	74.5	74.4	74.3	74.3	74.2	74.1	74.1	74.0	74.0

TABLE IIIC. ACCELERATED GIRLS. PERCENTAGES AND ESTIMATED MATURE HEIGHTS FOR GIRLS WITH SKELETAL AGES ONE YEAR OR MORE ADVANCED OVER THEIR CHRONOLOGICAL AGES:

SKELETAL AGES 7 THROUGH 11 YEARS

Skeletal Age	7-0	7-3	7-6	**7-10**	8-0	8-3	8-6	**8-10**	9-0	9-3	9-6	9-9	**10-0**	10-3	10-6	10-9	**11-0**	11-3	11-6	11-9
% of Mature Height	71.2	72.2	73.2	74.2	75.0	76.0	77.1	78.4	79.0	80.0	80.9	81.9	82.8	84.1	85.6	87.0	88.3	88.7	89.1	89.7
Ht. (inches)																				
37	52.0	51.2																		
38	53.4	52.6	51.9	51.2																
39	54.8	54.0	53.3	52.6	52.0	51.3														
40	56.2	55.4	54.6	53.9	53.3	52.6	51.9	51.0												
41	57.6	56.8	56.0	55.3	54.7	53.9	53.2	52.3	51.9	51.3										
42	59.0	58.2	57.4	56.6	56.0	55.3	54.5	53.6	53.2	52.5	51.9	51.3								
43	60.4	59.6	58.7	58.0	57.3	56.6	55.8	54.8	54.4	53.8	53.2	52.5	51.9	51.1						
44	61.8	60.9	60.1	59.3	58.7	57.9	57.1	56.1	55.7	55.0	54.4	53.7	53.1	52.3	51.4					
45	63.2	62.3	61.5	60.6	60.0	59.2	58.4	57.4	57.0	56.3	55.6	54.9	54.3	53.5	52.6	51.7	51.0			
46	64.6	63.7	62.8	62.0	61.3	60.5	59.7	58.7	58.2	57.5	56.9	56.2	55.6	54.7	53.7	52.9	52.1	51.9	51.6	51.3
47	66.0	65.1	64.2	63.3	62.7	61.8	61.0	59.9	59.5	58.8	58.1	57.4	56.8	55.9	54.9	54.0	53.2	53.0	52.7	52.4
48	67.4	66.5	65.6	64.7	64.0	63.2	62.3	61.2	60.8	60.0	59.3	58.6	58.0	57.1	56.1	55.2	54.4	54.1	53.9	53.5
49	68.8	67.9	66.9	66.0	65.3	64.5	63.6	62.5	62.0	61.3	60.6	59.8	59.2	58.3	57.2	56.3	55.5	55.2	55.0	54.6
50	70.2	69.3	68.3	67.4	66.7	65.8	64.9	63.8	63.3	62.5	61.8	61.1	60.4	59.5	58.4	57.5	56.6	56.4	56.1	55.7
51	71.6	70.6	69.7	68.7	68.0	67.1	66.1	65.1	64.6	63.8	63.0	62.3	61.6	60.6	59.6	58.6	57.8	57.5	57.2	**56.9**
52	73.0	72.0	71.0	70.1	69.3	68.4	67.4	66.3	65.8	65.0	64.3	63.5	62.8	61.8	60.7	59.8	58.9	58.6	58.4	58.0
53	74.4	73.4	72.4	71.4	70.7	69.7	68.7	67.6	67.1	66.3	65.5	64.7	64.0	63.0	61.9	60.9	60.0	59.8	59.5	59.1
54		74.8	73.8	72.8	72.0	71.1	70.0	68.9	68.4	67.5	66.7	65.9	65.2	64.2	63.1	62.1	61.2	60.9	60.6	60.2
55				74.1	73.3	72.4	71.3	70.2	69.6	68.8	68.0	67.2	66.4	65.4	64.3	63.2	62.3	62.0	61.7	61.3
56					74.7	73.7	72.6	71.4	70.9	70.0	69.2	68.4	67.6	66.6	65.4	64.4	63.4	63.1	62.8	62.4
57							73.9	72.7	72.2	71.3	70.5	69.6	68.8	67.8	66.6	65.5	64.6	64.3	64.0	63.5
58								74.0	73.4	72.5	71.7	70.8	70.0	69.0	67.8	66.7	65.7	65.4	65.1	64.7
59									74.7	73.8	72.9	72.0	71.3	70.2	68.9	67.8	66.8	66.5	66.2	65.8
60											74.2	73.3	72.5	71.3	70.1	69.0	68.0	67.6	67.3	66.9
61												74.5	73.7	72.5	71.3	70.1	69.1	68.8	68.5	68.0
62													74.9	73.7	72.4	71.3	70.2	69.9	69.6	69.1
63														74.9	73.6	72.4	71.3	71.0	70.7	70.2
64															74.8	73.6	72.5	72.2	71.8	71.3
65																74.7	73.6	73.3	72.9	72.5
66																	74.7	74.4	74.1	73.6
67																				74.7

TABLE IIID. ACCELERATED GIRLS. PERCENTAGES AND ESTIMATED MATURE HEIGHTS FOR GIRLS WITH SKELETAL AGES ONE YEAR OR MORE ADVANCED OVER THEIR CHRONOLOGICAL AGES:

SKELETAL AGES 12 THROUGH 17 YEARS

Skeletal Age	**12-0**	12-3	12-6	12-9	**13-0**	13-3	13-6	13-9	**14-0**	14-3	14-6	14-9	**15-0**	15-3	15-6	15-9	**16-0**	16-3	16-6	16-9	**17-0**	17-6
% of Mature Height	90.1	91.3	92.4	93.5	94.5	95.5	96.3	96.8	97.2	97.7	98.0	98.3	98.6	98.8	99.0	99.2	99.3	99.4	99.5	99.7	99.8	99.95
Ht. (inches)																						
46	51.1																					
47	52.2	51.5																				
48	53.3	52.6	51.9	51.3																		
49	54.4	53.7	53.0	52.4	51.9	51.3	50.9															
50	55.5	54.8	54.1	53.5	52.9	52.4	51.9	51.7	51.4	51.2	51.0											
51	56.6	55.9	55.2	54.5	54.0	53.4	53.0	52.7	52.5	52.2	52.0	51.9	51.7	51.6	51.5	51.4	51.4	51.3	51.3	51.2	51.1	51.0
52	57.7	57.0	56.3	55.6	55.0	54.5	54.0	53.7	53.5	53.2	53.1	52.9	52.7	52.6	52.5	52.4	52.4	52.3	52.3	52.2	52.1	52.0
53	58.8	58.1	57.4	56.7	56.1	55.5	55.0	54.8	54.5	54.2	54.1	53.9	53.8	53.6	53.5	53.4	53.4	53.3	53.3	53.2	53.1	53.0
54	59.9	59.1	58.4	57.8	57.1	56.5	56.1	55.8	55.6	55.3	55.1	54.9	54.8	54.7	54.5	54.4	54.4	54.3	54.3	54.2	54.1	54.0
55	61.0	60.2	59.5	58.8	58.2	57.6	57.1	56.8	56.6	56.3	56.1	56.0	55.8	55.7	55.5	55.4	55.4	55.3	55.3	55.2	55.1	55.0
56	62.2	61.3	60.6	59.9	59.3	58.6	58.2	57.9	57.6	57.3	57.1	57.0	56.8	56.7	56.5	56.5	56.4	56.3	56.3	56.2	56.1	56.0
57	63.3	62.4	61.7	61.0	60.3	59.7	59.2	58.9	58.6	58.3	58.2	58.0	57.8	57.7	57.6	57.5	57.4	57.3	57.3	57.2	57.1	57.0
58	64.4	63.5	62.8	62.0	61.4	60.7	60.2	59.9	59.7	59.4	59.2	59.0	58.8	58.7	58.6	58.5	58.4	58.3	58.3	58.2	58.1	58.0
59	65.5	64.6	63.9	63.1	62.4	61.8	61.3	61.0	60.7	60.4	60.2	60.0	59.8	59.7	59.6	59.5	59.4	59.4	59.3	59.2	59.1	59.0
60	66.6	65.7	64.9	64.2	63.5	62.8	62.3	62.0	61.7	61.4	61.2	61.0	60.9	60.7	60.6	60.5	60.4	60.4	60.3	60.2	60.1	60.0
61	67.7	66.8	66.0	65.2	64.6	63.9	63.3	63.0	62.8	62.4	62.2	62.1	61.9	61.7	61.6	61.5	61.4	61.4	61.3	61.2	61.1	61.0
62	68.8	67.9	67.1	66.3	65.6	64.9	64.4	64.0	63.8	63.5	63.3	63.1	62.9	62.8	62.6	62.5	62.4	62.4	62.3	62.2	62.1	62.0
63	69.9	69.0	68.2	67.4	66.7	66.0	65.4	65.1	64.8	64.5	64.3	64.1	63.9	63.8	63.6	63.5	63.4	63.4	63.3	63.2	63.1	63.0
64	71.0	70.1	69.3	68.4	67.7	67.0	66.5	66.1	65.8	65.5	65.3	65.1	64.9	64.8	64.6	64.5	64.4	64.4	64.3	64.2	64.1	64.0
65	72.1	71.2	70.3	69.5	68.8	68.1	67.5	67.1	66.9	66.5	66.3	66.1	65.9	65.8	65.7	65.5	65.5	65.4	65.3	65.2	65.1	65.0
66	73.3	72.3	71.4	70.6	69.8	69.1	68.5	68.2	67.9	67.6	67.3	67.1	66.9	66.8	66.7	66.5	66.5	66.4	66.3	66.2	66.1	66.0
67	74.4	73.4	72.5	71.7	70.9	70.2	69.6	69.2	68.9	68.6	68.4	68.2	68.0	67.8	67.7	67.5	67.5	67.4	67.3	67.2	67.1	67.0
68		74.5	73.6	72.7	72.0	71.2	70.6	70.2	70.0	69.6	69.4	69.2	69.0	68.8	68.7	68.6	68.5	68.4	68.3	68.2	68.1	68.0
69			74.7	73.8	73.0	72.3	71.7	71.3	71.0	70.6	70.4	70.2	70.0	69.8	69.7	69.6	69.5	69.4	69.3	69.2	69.1	69.0
70				74.9	74.1	73.3	72.7	72.3	72.0	71.6	71.4	71.2	71.0	70.8	70.7	70.6	70.5	70.4	70.3	70.2	70.1	70.0
71						74.3	73.7	73.3	73.0	72.7	72.4	72.2	72.0	71.9	71.7	71.6	71.5	71.4	71.4	71.2	71.1	71.0
72							74.8	74.4	74.1	73.7	73.5	73.2	73.0	72.9	72.7	72.6	72.5	72.4	72.4	72.2	72.1	72.0
73										74.7	74.5	74.3	74.0	73.9	73.7	73.6	73.5	73.4	73.4	73.2	73.1	73.0
74														74.9	74.4	74.6	74.5	74.4	74.4	74.2	74.1	74.0

TABLE IIIE. RETARDED GIRLS. PERCENTAGES AND ESTIMATED MATURE HEIGHTS FOR GIRLS WITH SKELETAL AGES ONE YEAR OR MORE RETARDED FOR THEIR CHRONOLOGICAL AGES:

SKELETAL AGES 6 THROUGH 11 YEARS

Skeletal Age	6-0	6-3	6-6	**6-10**	7-0	7-3	7-6	**7-10**	8-0	8-3	8-6	**8-10**	9-0	9-3	9-6	9-9	**10-0**	10-3	10-6	10-9	**11-0**	11-3	11-6	11-9
% of Mature Height	73.3	74.2	75.1	76.3	77.0	77.9	78.8	79.7	80.4	81.3	82.3	83.6	84.1	85.1	85.8	86.6	87.4	88.4	89.6	90.7	91.8	92.2	92.6	92.9
Ht. (inches)																								
38	51.8	51.2																						
39	53.2	52.6	51.9	51.1																				
40	54.6	53.9	53.3	52.4	51.9	51.3																		
41	55.9	55.3	54.6	53.7	53.2	52.6	52.0	51.4																
42	57.3	56.6	55.9	55.0	54.5	53.9	53.3	52.7	52.2	51.7	51.0													
43	58.7	58.0	57.3	56.4	55.8	55.2	54.6	54.0	53.5	52.9	52.2	51.4	51.1											
44	60.0	59.3	58.6	57.7	57.1	56.5	55.8	55.2	54.7	54.1	53.5	52.6	52.3	51.7	51.3									
45	61.4	60.6	59.9	59.0	58.4	57.8	57.1	56.5	56.0	55.4	54.7	53.8	53.5	52.9	52.4	52.0	51.5							
46	62.8	62.0	61.3	60.3	59.7	59.1	58.4	57.7	57.2	56.6	55.9	55.0	54.7	54.1	53.6	53.1	52.6	52.0	51.3					
47	64.1	63.3	62.6	61.6	61.0	60.3	59.6	59.0	58.5	57.8	57.1	56.2	55.9	55.2	54.8	54.3	53.8	53.2	52.5	51.8	51.2	51.0		
48	65.5	64.7	63.9	62.9	62.3	61.6	60.9	60.2	59.7	59.0	58.3	57.4	57.1	56.4	55.9	55.4	54.9	54.3	63.6	52.9	52.3	52.1	51.8	51.7
49	66.9	66.0	65.2	64.2	63.6	62.9	62.2	61.5	60.9	60.3	59.5	58.6	58.3	57.6	57.1	56.6	56.1	55.4	54.7	54.0	53.4	53.1	52.9	52.7
50	68.2	67.4	66.6	65.5	64.9	64.2	63.5	62.7	62.2	61.5	60.8	59.8	59.5	58.8	58.3	57.7	57.2	56.6	55.8	55.1	54.5	54.2	54.0	53.8
51	69.6	68.7	67.9	66.8	66.2	65.5	64.7	64.0	63.4	62.7	62.0	61.0	60.6	59.9	59.4	58.9	58.4	57.7	56.9	56.2	55.6	55.3	55.1	54.9
52	70.9	70.1	69.2	68.2	67.5	66.8	66.0	65.2	64.7	64.0	63.2	62.2	61.8	61.1	60.6	60.0	59.5	58.8	58.0	57.3	56.6	56.4	56.2	56.0
53	72.3	71.4	70.6	69.5	68.8	68.0	67.3	66.5	65.9	65.2	64.4	63.4	63.0	62.3	61.8	61.2	60.6	60.0	59.2	58.4	57.7	57.5	57.2	57.1
54	73.7	72.8	71.9	70.8	70.1	69.3	68.5	67.8	67.2	66.4	65.6	64.6	64.2	63.5	62.9	62.4	61.8	61.1	60.3	59.5	58.8	58.6	58.3	58.1
55		74.1	73.2	72.1	71.4	70.6	69.8	69.0	68.4	67.7	66.8	65.8	65.4	64.6	64.1	63.5	62.9	62.2	61.4	60.6	59.9	59.7	59.4	59.2
56			74.6	73.4	72.7	71.9	71.1	70.3	69.7	68.9	68.0	67.0	66.6	65.8	65.3	64.7	64.1	63.3	62.5	61.7	61.0	60.7	60.5	60.3
57				74.7	74.0	73.2	72.3	71.5	70.9	70.1	69.3	68.2	67.8	67.0	66.4	65.8	65.2	64.5	63.6	62.8	62.1	61.8	61.6	61.4
58						74.5	73.6	72.8	72.1	71.3	70.5	69.4	69.0	68.2	67.6	67.0	66.4	65.6	64.7	63.9	63.2	62.9	62.6	62.4
59							74.9	74.0	73.4	72.6	71.7	70.6	70.2	69.3	68.8	68.1	67.5	66.7	65.8	65.0	64.3	64.0	63.7	63.5
60									74.6	73.8	72.9	71.8	71.3	70.5	69.9	69.3	68.7	67.9	67.0	66.2	65.4	65.1	64.8	64.6
61											74.1	73.0	72.5	71.7	71.1	70.4	69.8	69.0	68.1	67.3	66.4	66.2	65.9	65.7
62												74.2	73.7	72.9	72.3	71.6	70.9	70.1	69.2	68.4	67.5	67.2	67.0	66.7
63													74.7	74.0	73.4	72.7	72.1	71.3	70.3	69.5	68.6	68.3	68.0	67.8
64															74.6	73.9	73.2	72.4	71.4	70.6	69.7	69.4	69.1	68.9
65																	74.4	73.5	72.5	71.7	70.8	70.5	70.2	70.0
66																		74.7	73.7	72.8	71.9	71.6	71.3	71.0
67																			74.8	73.9	73.0	72.7	72.4	72.1
68																					74.1	73.8	73.4	73.2
69																						74.8	74.5	74.3

TABLE IIIF. RETARDED GIRLS. PERCENTAGES AND ESTIMATED MATURE HEIGHTS FOR GIRLS WITH SKELETAL AGES ONE YEAR OR MORE RETARDED FOR THEIR CHRONOLOGICAL AGES:

SKELETAL AGES 12 THROUGH 17 YEARS

Skeletal Age	12-0	12-3	12-6	12-9	13-0	13-3	13-6	13-9	14-0	14-3	14-6	14-9	15-0	15-3	15-6	15-9	16-0	16-3	16-6	16-9	17-0
% of Mature Height	93.2	94.2	94.9	95.7	96.4	97.1	97.7	98.1	98.3	98.6	98.9	99.2	99.4	99.5	99.6	99.7	99.8	99.9	99.9	99.95	100.0
Ht. (inches)																					
48	51.5	51.0																			
49	52.6	52.0	51.6	51.2																	
50	53.6	53.1	52.7	52.2	51.9	51.5	51.2	51.0													
51	54.7	54.1	53.7	53.3	52.9	52.5	52.2	52.0	51.9	51.7	51.6	51.4	51.3	51.3	51.2	51.2	51.1	51.1	51.1	51.0	51.0
52	55.8	55.2	54.8	54.3	53.9	53.6	53.2	53.0	52.9	52.7	52.6	52.4	52.3	52.3	52.2	52.2	52.1	52.1	52.1	52.0	52.0
53	56.9	56.3	55.8	55.4	55.0	54.6	54.2	54.0	53.9	53.8	53.6	53.4	53.3	53.3	53.2	53.2	53.1	53.1	53.1	53.0	53.0
54	57.9	57.3	56.9	56.4	56.0	55.6	55.3	55.0	54.9	54.8	54.6	54.4	54.3	54.3	54.2	54.2	54.1	54.1	54.1	54.0	54.0
55	59.0	58.4	58.0	57.5	57.1	56.6	56.3	56.1	56.0	55.8	55.6	55.4	55.3	55.3	55.2	55.2	55.1	55.1	55.1	55.0	55.0
56	60.1	59.4	59.0	58.5	58.1	57.7	57.3	57.1	57.0	56.8	56.6	56.5	56.3	56.3	56.2	56.2	56.1	56.1	56.1	56.0	56.0
57	61.2	60.5	60.1	59.6	59.1	58.7	58.3	58.1	58.0	57.8	57.6	57.5	57.3	57.3	57.2	57.2	57.1	57.1	57.1	57.0	57.0
58	62.2	61.6	61.1	60.6	60.2	59.7	59.4	59.1	59.0	58.8	58.6	58.5	58.3	58.3	58.2	58.2	58.1	58.1	58.1	58.0	58.0
59	63.3	62.6	62.2	61.7	61.2	60.8	60.4	60.1	60.0	59.8	59.7	59.5	59.4	59.3	59.2	59.2	59.1	59.1	59.1	59.0	59.0
60	64.4	63.7	63.2	62.7	62.2	61.8	61.4	61.2	61.0	60.9	60.7	60.5	60.4	60.3	60.2	60.2	60.1	60.1	60.1	60.0	60.0
61	65.5	64.8	64.3	63.7	63.3	62.8	62.4	62.2	62.1	61.9	61.7	61.5	61.4	61.3	61.2	61.2	61.1	61.1	61.1	61.0	61.0
62	66.5	65.8	65.3	64.8	64.3	63.9	63.5	63.2	63.1	62.9	62.7	62.5	62.4	62.3	62.2	62.2	62.1	62.1	62.1	62.0	62.0
63	67.6	66.9	66.4	65.8	65.3	64.9	64.5	64.2	64.1	63.9	63.7	63.5	63.4	63.3	63.3	63.2	63.1	63.1	63.1	63.0	63.0
64	68.7	67.9	67.4	66.9	66.4	65.9	65.5	65.2	65.1	64.9	64.7	64.5	64.4	64.3	64.3	64.2	64.1	64.1	64.1	64.0	64.0
65	69.7	69.0	68.5	67.9	67.4	66.9	66.5	66.3	66.1	65.9	65.7	65.5	65.4	65.3	65.3	65.2	65.1	65.1	65.1	65.0	65.0
66	70.8	70.1	69.5	69.0	68.5	68.0	67.6	67.3	67.1	66.9	66.7	66.5	66.4	66.3	66.3	66.2	66.1	66.1	66.1	66.0	66.0
67	71.9	71.1	70.6	70.0	69.5	69.0	68.6	68.3	68.2	68.0	67.7	67.5	67.4	67.3	67.3	67.2	67.1	67.1	67.1	67.0	67.0
68	73.0	72.2	71.7	71.1	70.5	70.0	69.6	69.3	69.2	69.0	68.8	68.6	68.4	68.3	68.3	68.2	68.1	68.1	68.1	68.0	68.0
69	74.0	73.2	72.7	72.1	71.6	71.1	70.6	70.3	70.2	70.0	69.8	69.6	69.4	69.3	69.3	69.2	69.1	69.1	69.1	69.0	69.0
70		74.3	73.8	73.1	72.6	72.1	71.6	71.4	71.2	71.0	70.8	70.6	70.4	70.4	70.3	70.2	70.1	70.1	70.1	70.0	70.0
71			74.8	74.2	73.6	73.1	72.7	72.4	72.2	72.0	71.8	71.6	71.4	71.4	71.3	71.2	71.1	71.1	71.1	71.0	71.0
72					74.7	74.2	73.7	73.4	73.3	73.0	72.8	72.6	72.4	72.4	72.3	72.2	72.1	72.1	72.1	72.0	72.0
73							74.7	74.4	74.3	74.0	73.8	73.6	73.4	73.4	73.3	73.2	73.1	73.1	73.1	73.0	73.0
74											74.8	74.6	74.4	74.4	74.3	74.2	74.1	74.1	74.1	74.0	74.0

ards for hands, with the expectation that they will be used in conjunction with these standards. They have not been tested for readings made from other areas of the skeleton, or other methods of assessing degree of skeletal maturing. Such usage might yield less accurate predictions.*

(c) Also, there is some inaccuracy in measurements of height. Both diurnal variations in stature, and careless measuring techniques, could account for some of the error in prediction.

Aside from these technical factors, we must consider the variations in children's developmental processes. Patterns of growth may be influenced to some extent by illnesses, accidents, changes in diet, or certain hormone imbalances. For these reasons one must, in clinical practice, assess every prediction of future growth against the background of all available knowledge about the particular child and his own growth history.[8]

In setting up the tables it has been necessary to take into consideration the differences in growth rates of accelerated and retarded children. In general, there is a relationship between the intensities of maturation and growth. Children who are accelerated in physical maturity tend to grow with exceptional vigor, and children who are retarded in their maturation tend to grow in a more subdued manner than the average. As a result, the accelerated child, though he has achieved a greater PMH than the average child his age, will have achieved less than the average for his skeletal age. Conversely, the retarded child, though behind his age peers, will be closer to his eventual height than the average for his degree of skeletal maturity. In other words, the younger the child for a given SA the more chance he has for further growth.

The supplementary tables take care of the differences in growth rate for the ages where the predictions will be affected. For example, at 10 years the average girl has completed 86.2 per cent of her eventual height; but the accelerated 8½-year-old with an SA of 10 years has completed 82.8 per cent, and the retarded 12-year-old with an SA of 10 years has achieved 87.4 per cent of her adult stature. The percentages for these deviant cases may be compared with the normal expectancy for their chronological ages: 81.0 per cent at 8½ and 92.2 per cent at 12. Even these supplementary tables may not be adequate for the more extreme deviates. The children who are retarded more than two years will probably reach shorter adult heights, and those who are accelerated more than two years are likely to become taller than the prediction tables indicate.

The need for supplementary tables is probably also related to the fact that the development of the skeleton is only one part of the process of physical maturation, and is not perfectly correlated with the other parts. Those children selected as most retarded (or advanced) in one area are likely to be somewhat nearer the average in the other areas. Therefore, a fair proportion of the children selected as skeletally deviant can be expected to have a *general* physical maturity age which

*The accuracy of determination of skeletal age, and hence of prediction, should however be increased by the inclusion of additional areas of the skeleton, if the skeletal ages for these other areas were derived in the same manner as the hands (Bayley,[4] Simmons[5]).

TABLE IV. MEANS AND STANDARD DEVIATIONS OF THE ERRORS IN PREDICTION OF HEIGHT FOR TWO GROUPS OF GIRLS

AGE IN YEARS AND MONTHS	STANDARDIZATION SAMPLE*			VALIDATING SAMPLE†		
	NO. OF CASES	MEAN	S.D	NO. OF CASES	MEAN	S.D
8-0	20	−.12	1.18	20	−.86	1.73
8-6	34	+.12	1.09			
9-0	47	−.09	1.13	20	−.65	1.46
9-6	56	−.11	1.10	20	−.58	1.33
10-0	65	−.01	1.15	22	−.49	1.37
10-6	74	+.09	1.16	21	−.37	1.20
11-0	77	+.10	1.09	21	−.36	1.15
11-6	76	+.21	.97	21	−.22	.94
12-0	79	+.18	.92	21	−.13	1.06
12-6	75	+.07	.89	21	−.09	.78
13-0	78	+.01	.72	18	−.21	.62
13-6	77	−.03	.55	18	−.15	.55
14-0	77	−.03	.48	18	+.10	.42
14-6	71	−.02	.37	19	+.001	.40
15-0	72	+.03	.29	19	+.08	.38
15-6	58	−.03	.26	21	+.04	.32
16-0	63	−.02	.24	21	−.02	.26
16-6	59	−.02	.02	16	−.07	.25
17-0	63	−.02	.02	18	+.02	.20
17-6	46	−.02	.01	10	−.08	.22
18-0				11	−.05	.11

*The Guidance Study.
†The Berkeley Growth Study.

TABLE V. MEANS AND STANDARD DEVIATIONS OF THE ERRORS IN PREDICTION OF HEIGHT FOR TWO GROUPS OF BOYS

AGE IN YEARS AND MONTHS	STANDARDIZATION SAMPLE*			VALIDATING SAMPLE†		
	NO. OF CASES	MEAN	S.D	NO. OF CASES	MEAN	S.D
8-0	15	+.05	1.62	21	−.13	1.47
8-6	26	+.17	1.84			
9-0	36	−.24	2.10	20	+.02	1.27
9-6	43	+.14	1.89	20	−.41	1.13
10-0	53	+.20	1.45	20	+.002	1.33
10-6	56	+.01	1.49	21	+.06	1.11
11-0	57	+.01	1.98	22	−.04	1.14
11-6	52	+.01	1.41	22	−.12	1.15
12-0	54	+.07	1.49	19	+.16	1.09
12-6	52	−.05	1.45	20	+.23	1.09
13-0	54	−.11	1.79	22	+.01	1.21
13-6	53	−.18	1.14	20	+.05	1.32
14-0	52	−.04	1.06	20	+.13	1.21
14-6	50	+.03	.91	20	−.23	.85
15-0	52	+.01	.59	20	+.03	.88
15-6	47	+.02	.46	21	+.07	.65
16-0	44	+.01	.28	22	+.01	.49
16-6	45	+.02	.29	18	+.12	.35
17-0	44	+.02	.26	20	+.19	.41
17-6	33	−.05	.21	20	+.14	.30
18-0				16	+.14	.38

*The Guidance Study.
†The Berkeley Growth Study.

is nearer the norm than is their SA. Whatever the reason, we find as a matter of practice, that accuracy of prediction is increased by use of the supplementary tables.

Tables IV and V give the actual error in prediction found for two groups of normal Berkeley, Calif., children. These predictions are based on Greulich-Pyle skeletal ages and the single x-ray and height measurement made before 12 or 14 years. After these ages the error in prediction on single x-rays is rapidly reduced to less than half an inch for the majority of children. This is illustrated in Fig. 2 for one normal boy. His growth in height has been plotted in two ways, by his chronological age (solid line) and by his SA (broken line). He is

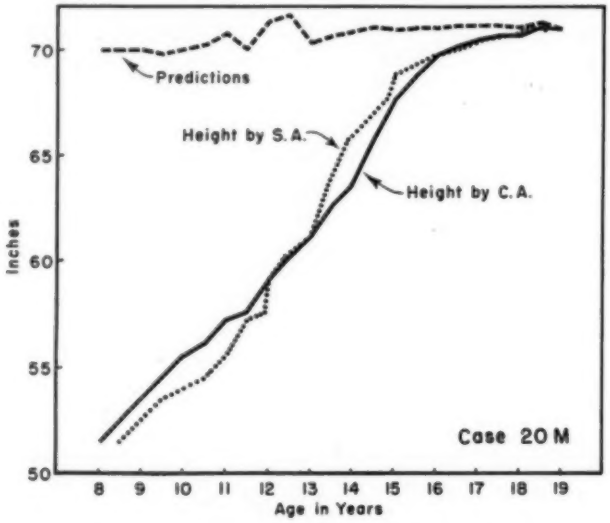

Fig. 2.—The growth record of one boy. Height is plotted by chronological age (solid line) and by skeletal age (dotted line). Successive predictions of adult height are shown in the broken line.

percentages given in the appropriate prediction tables. The data from the larger sample were used in constructing the tables, and therefore the mean error for this group should be very small. The smaller Berkeley Growth Study group forms an independent validating sample. Through 12 years in the girls, and 14 years in the boys, the standard deviations are approximately one inch or a little larger. That is, about two-thirds of the children grew to a height which varied an inch or less from the prediction made on a slightly accelerated in skeletal maturity before 11 years, and slightly retarded for a period after 13 years. The heights predicted at each age are shown in the almost horizontal line across the top. The early estimates for this boy are a little short, and there is some fluctuation between 9 and 14 years, but after 14 the predictions become very stable and accurate.

In practice the accuracy of estimates on a given child can be greatly increased by taking repeated x-rays over a period of time. The *trends* of the

child's growth can then be evaluated in the light of other knowledge about him.

In general, the accuracy of prediction from the new tables for Greulich-Pyle SA's compares favorably with the prediction tables for the Todd SA's published in 1946.[1]

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INCONTINENTIA PIGMENTI

A Report of Three Additional Cases

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INCONTINENTIA pigmenti is a relatively rare pigmentary anomaly of the skin. The first recorded instance of the disease under this name was the case presentation by Bloch[1] and this was followed by an extensive study of the condition by Sulzberger.[2] Naegeli[3] reported on three patients (a father and two daughters) and Almkvist (quoted by Sulzberger[2]) described another patient with the same condition. Additional reports have been published by Sulzberger,[6] Hopkins and Machacek,[7] Doornink,[8] Pierini, Jarcia, and Pomposiello,[14] and Stringa, Pomposiello and Badaraco.[15]

The eruption appears at birth or in the first few weeks or months of life, although, according to Nexmand,[9] his patient did not develop her eruption until she was 7 years old. The condition is characterized by bizarre, irregularly shaped areas of brown or slate pigmentation. The outlines of the pigmented patches may be spidery or may take on the appearance of colored veins in marbles. In some of the patients, the pigmentary changes were preceded by inflammatory eruptions of the skin. The pigmented areas may be slightly elevated or depressed and are most marked on the trunk. The extremities are not uncommonly affected and the face is usually spared.

There is some controversy regarding the explanation for the bizarre distribution of the pigment. Hopkins is of the opinion that many of the chromatophores lie in the perivascular spaces and wander out along the lymphatic channels. Sulzberger, however, believes that the chromatophores are irregularly distributed and do not follow the course of the vessels or nerves. The color will depend on the location of the melanin in the cutis as well as the thickness and degree of pigmentation of the overlying epidermis. When the patients were observed over a period of several years, it was noted that some areas of pigmentation tend to become fainter, smaller, and at times even disappear.

Many of the authors[1, 4, 10, 11] describe concomitant congenital abnormalities, most of them concerned with ectodermal structures. They may occur in the patients as well as in other members of the same family.[2, 10] These anomalies include detachment of the retina, retrobulbar glioma, bilateral convergent strabismus, blindness of one eye, mental abnormality, Little's disease of the tetraplegic type, congenital cardiac disease, thin hair, patchy alopecia associated with a scleraderma-like consistency of the scalp as seen in "coup de sabre," and malformation of teeth and nails. Most of the authors fail to mention investigations of siblings or progenitors. None of the females had offsprings at the time their cases were recorded in

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the literature as all but one were too young to have any children.

Although it seems established that the condition is a congenital anomaly, it should be pointed out that in some patients the pigmentary changes followed inflammatory processes of the skin. In fact, some described a preceding inflammatory stage[11, 12] on which vesicles and verruca-like lesions[10] were superimposed. It is possible that trauma or other intra- and extrauterine toxic factors may damage the basal cells, thereby allowing a greater permeability of the cell-membrane for melanin. This concept seems to be confirmed by the appearance of alterations in some of the basal cells. The epidermis overlying the pigmented areas is usually devoid of pigment and similar "downward dropping of pigment" is sometimes observed in tar, arsenic, and x-ray pigmentations. It is generally agreed that the disease is due to a dropping down of pigment from the epidermis into the cutis. Bloch and Sulzberger called the condition "incontinentia pigmenti" since they felt that the epidermis had become incontinent of its own pigment and allowed for it to descend into the cutis. Siemens[4] suggested the name "melanosis corii degenerativa" since he felt that the condition was primarily concerned with degenerative changes in the epidermis which permitted the loss of pigment, and its migration into the cutis. Other authors considered the condition a purely nevoid one and proposed the names "familial chromatophore nevus"[3] and "nevus reticularis et pigmentosus."[5] Doornink believes that this condition should be considered as a nonspecific anatomopathologic entity, since this type of anomaly has also been observed in many other dermatoses including lupus erythematosus, parapsoriasis, and lichen planus. An important contribution to the literature on the subject of incontinentia pigmenti was made by Carney[13] who reported five cases and reviewed the existing literature on this pigmentary anomaly and the associated developmental anomalies in the patients and their families. The author stresses the three phases of the disease (bullous, inflammatory, and verrucous) and describes in detail the histopathologic findings in all three stages. According to Carney the bullous phase is so typical that the diagnosis can be made during this stage prior to the deposition of the pigment.

From a perusal of the literature there is a general agreement regarding the histopathologic findings. In the epidermis the changes are minimal and limited to the basal cells which show various degrees of irregularity and hydrops of the individual cells. The protoplasm of these cells is vacuolized, and the nuclei are irregular in outline, deeply stained, and smaller than normal nuclei. The pigment in the basal cells is usually not increased and in some instances is entirely lacking. There is an increase of connective tissue cells in the cutis, especially in those areas where there are large masses of pigment. There is usually some perivascular infiltrate consisting predominantly of plasma cells and lymphocytes. Most of the pigment occurs as large masses in the papillae, but it may also be present in the reticular layer especially around the vessels. In some instances, a certain amount of pigment is present in the endothelium of the blood vessels and according to Sulzberger, some of the pigment is in the lumen of the vessels.

The pigmentation seen clinically is attributable to the pigment formed in the chromatophores of the upper and midportion of the cutis.

Finally it is worth while mentioning the idea of Heilesen[11] that incontinentia pigmenti may well be divided into stages. At first there are erythematous, often inflammatory lesions on which blisters may develop. As these subside, the more characteristic pigmentation of the next stage is found. The histologic picture may also tend to vary with the stage at which the biopsy is taken, showing more of an inflammatory reaction with increased edema and cellular infiltrate in the initial stage. Later there is only a slight cellular infiltrate, mostly around the collections of melanin pigment.

CASE REPORTS

CASE 1 (Loveman and Fliegelman).—W. L., a 2½-year-old white female. This was the mother's first pregnancy and the labor lasted nineteen hours but the delivery was uncomplicated. There was nothing significant in the family history. There were no defects noted in the parents of the child, nor was there any history of ectodermal defects elicited in other members of the family. Three days after birth, the hospital resident noted a "dry type of maculopapular skin rash" on the left arm and leg. Several days later she had a convulsion, and following a neurological examination and an electroencephalogram, a diagnosis of "focal and myoclonic epilepsy" was made. The child was started on pyribenzamine ointment and penicillin injections on Jan. 15, 1950, by the pediatrician who noted the eruption at that time consisted of "generalized confluent and discrete" lesions. On that same date she was given phenobarbital and Dilantin for her epilepsy.

When she was first seen by one of us on January 20, 34 days after birth, she presented numerous, thick-walled vesicles on her arms and legs, with nondescript, erythematous areas over the back and buttocks. A diagnosis of dermatitis medicamentosa and/or dermatitis venenata was entertained although the eruption was noted before any local or parenteral medication had been started. She was placed on medicated baths and calamine lotion locally. No other topical medication was used and these were soon discontinued since the lesions apparently remained asymptomatic. The patient has been maintained on phenobarbital ½ gr. b.i.d. and Dilantin 1½ gr. daily, and since October, 1950, she has also received Tridione 0.3 Gm. t.i.d. which keeps the epilepsy under control.

The patient was again seen by us at the age of 4 months. The skin lesions had for the most part become definitely pigmented in a bizarre, reticulated fashion. It was at this time that the diagnosis of incontinentia pigmenti was first entertained. A few scattered vesicles and several verrucous-like lesions over the left knee were seen (Fig. 1). A definite hirsutism of the vulvar area, probably due to the Dilantin therapy, was also present (Fig. 2).

Dentition was delayed, the first tooth appearing at the age of 10 months. While she had a full head of hair, its quality tended to be brittle and stringy. At the time she was last observed by us at the age of 19 months, she was still taking Dilantin, Tridione, and phenobarbital which were adequately controlling her seizures. All of the verrucous lesions had spontaneously disappeared. The reticulated, macular lesions were a dark brown and fewer in number. No vesicles were seen. She had very little vulvar hirsutism. Only two upper and three lower teeth had erupted.

Laboratory data and x-ray studies: Blood counts were normal and a blood Kahn negative. X-rays of the skull and long bones showed no abnormalities.

Histopathologic examination of a macular, pigmented area showed the typical changes of incontinentia pigmenti. There were few epidermal

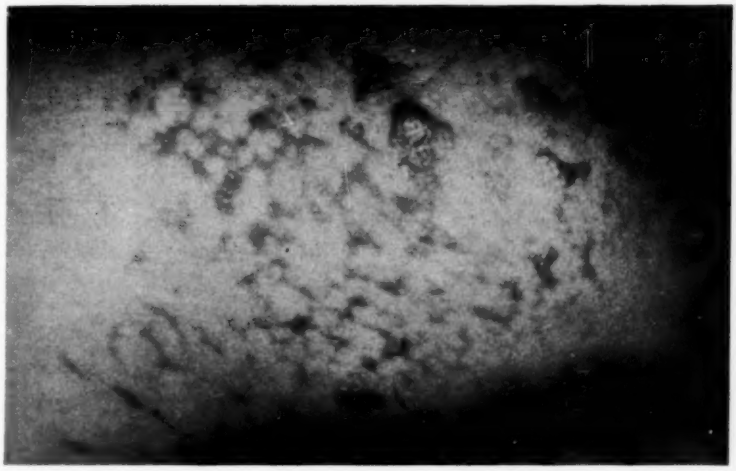

Fig. 1 (Case 1).—Note the bizarre distribution of the pigment and the verrucous-like lesions over the left knee.

Fig. 2 (Case 1).—Same case showing the pigmented areas and the vulvar hirsutism.

Fig. 3.

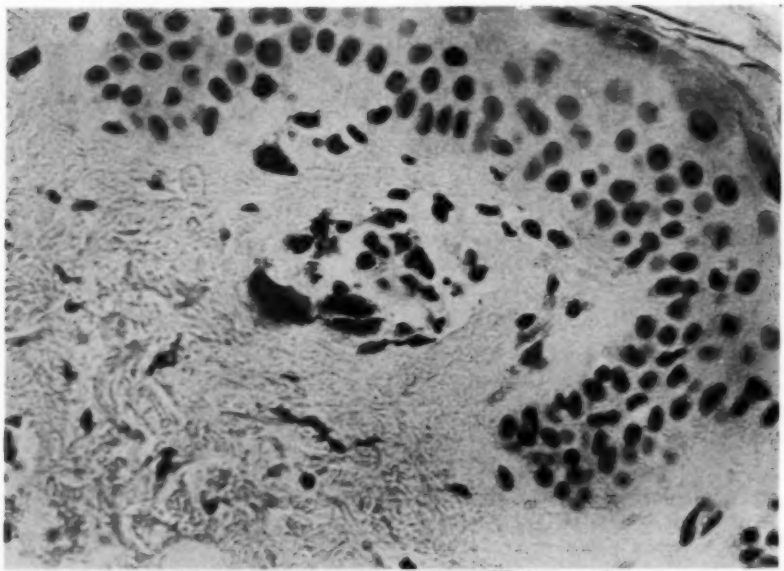

Fig. 4.

Fig. 3 (Case 1).—Histopathologic picture of incontinentia pigmenti showing a few inflammatory cells around the melanin-laden, phagocytic chromatophores.

Fig. 4 (Case 1).—Biopsy of the verruca-like lesions showing a marked epithelial hyperplasia, acanthosis, and edema in the upper corium.

changes consisting of some irregularity and hydrops in individual cells of the basal layer. In the upper corium there were a few inflammatory cells noted around the melanin-laden, phagocytic chromatophores (Fig. 3).

Histopathologic examination of a verrucous-like lesion showed increase in pigmentation in the upper corium, hyperkeratinization, marked epithelial hyperplasia, and an increase in the size of the rete pegs. There also appeared to be some abnormal cornification within some of the cells in the larger rete pegs. Some of the superficial corium in the papillae showed edema and in the upper corium there was some increase in blood vessels and a perivascular, lymphocytic infiltrate. There was also pigment found in chromatophores in the cutis. In the deeper portions of the corium there was a perivascular, lymphocytic infiltrate and the vessels showed some endothelial hyperplasia. No accessory skin structures were seen in the sections (Fig. 4).

We feel that the hypertrophic lesions are a component part of the eruption seen in incontinentia pigmenti. Clinically, however, the lesions did not resemble warts, in that they were relatively smooth in appearance (hence the absence of parakeratosis). Furthermore, the lesions arose from the typical pigmented lesions of incontinentia pigmenti and not from the normal appearing skin. There seemed to be a definite evolution of the lesions from the macular pigmented areas to the papular and then to the localized papulohypertrophic ones.

The hypertrophic lesions disappeared spontaneously as did the papular element in many of the reticulated lesions. Although a total of 100 r (in two doses) of superficial x-ray was given to one of the hypertrophic lesions, it was not felt that this played a significant part in its disappearance.

Case 2 (Weidman and Rein.—J. S., a 2½-year-old girl, was first seen by us on Oct. 31, 1950. Her mother stated that two days after birth the baby developed "a blistery rash" which remained for six weeks and left residual pigmentation and "lines." At the age of 14 months, an erythematous eruption appeared on the legs and disappeared without treatment. There was nothing significant in the family history. Father suffered from hay fever; mother was apparently well. The serologic test for syphilis in mother, father, maternal grandfather, and in the patient was negative.

Physical examination: The patient was a well-developed, fairly well-nourished child. The examination of the skin revealed the presence of pigmented areas from slate gray to bluish in color, distributed mostly over the trunk and extremities but sparing the face. The pigmentary disturbance was bizarre in outline (Fig. 5). In some areas it formed a network, in others it assumed a very irregular pattern comparable to branches of trees, spiders, or feathers. Besides the skin condition, a striking feature was the fact that the child did not seem to see well and approximated to the eyes the objects given or shown to her. There was a moderate degree of diffuse alopecia on the scalp. An ophthalmologic examination was performed by Dr. Louis R. Lang who reported as follows: "The visual acuity could not be elicited because of her age; however, a retinoscopic examination revealed a high degree of myopia. Fundus examination was extremely difficult. I was able to see the optic disc which was pale and showed a marked degree of stretching characteristic of myopia. Throughout the fundus there are numerous patches of pigment, varying in size, situated either in the retina or in the choroid."

A biopsy specimen was taken from a pigmented lesion on the patient's thigh and the histopathologic picture as described by Dr. Max Jessner was as follows: "The horny layer is lamellous and somewhat enlarged. The epidermis is normal except that no pigment could be found in the basal cell layer and higher up. There is some inflammatory infiltration around the vessels of the uppermost part of the

cutis and one sees in places massed pigment which is partly contained in chromatophores (Figs. 7 and 8). Where it is more clumpy, it is impossible to make out whether it is intra- or extracellular. Diagnosis: Compatible with incontinentia pigmenti."

Dental examination: The patient was examined by Dr. A. George Beck, who stated the following: "The child's mouth presents a retarded development evidence of soft tissue pathology. Child gives the impression of being a mouth breather which may be due to the narrow nasal passages caused by a crowded arch."

In October, 1950, an area the size of a quarter was treated with 50 per cent trichloracetic acid in order to determine whether there would be any change in the pigmentation. When

Fig. 5 (Case 2).—Showing the distribution of pigment in form of lines and zigzags on the posterior surface of the lower extremities.

Fig. 6 (Case 2).—Note among the pigmented areas on the right flank a small area to which trichloracetic acid was applied. The spot which was intensely pigmented before the treatment became pink and was deprived of pigment

of at least 6 months. Teeth are crowded and in malocclusion, underdeveloped in size, and give a white, chalklike appearance. The upper and lower arches are very small and narrow and seem to correspond to the narrow structure of the face. Palate presents a very narrow vault, suggestive of a tendency to an arrested cleft palate with lateral walls deeply convex toward the median line. There is no

observed on Jan. 3, 1951, it was seen that the inflammatory reaction which followed the application of the caustic subsided and the area lost its pigment and became pink.

The child developed an upper respiratory infection for which her family physician prescribed penicillin, terramycin, and aspirin. This was fol-

Fig. 7.

Fig. 8.

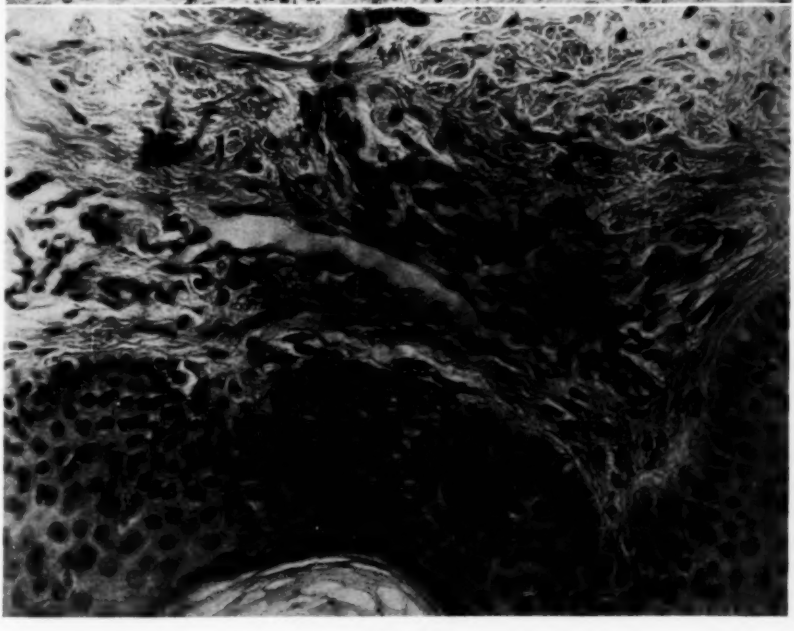

Fig. 7 (Case 2).—Showing an inflammatory infiltrate around the vessels and massed pigment partly contained in chromatophores. (×247.5.)

Fig. 8 (Case 2).—Magnification of the preceding figure showing in more detail the perivascular inflammatory infiltrate and the melanin-laden chromatophores.

lowed by an erythematous eruption limited entirely to the pigmented areas which, according to the mother, were accentuated and raised. When the child was seen several days later, the pigmented areas were still accentuated and raised, especially on the lower extremities.

CASE 3 (From the New York Skin and Cancer Unit, Service of Dr. Frances Pascher).—R. R., a white 2-year-old girl. There was nothing significant in the history. There was no consanguinity of the parents. No similar conditions were observed in the family. Immediately after birth, the patient developed an eruption characterized by bullae and vesicular lesions. The condition was diagnosed at that time as "exudative diathesis." The above eruption was followed by slate gray and brownish pigmentations involving all parts of the body including the scalp, face, and arms. Later, some of the areas lost most of their pigmentation; in other areas the pigmentation became paler.

The residual pigmented areas were arranged in patches, stripes, netlike patterns, and many small, irregularly shaped spots which looked as if they were splashed on the skin. The larger lesions on the legs and some smaller ones on the trunk seemed to be slightly firmer than the normal skin and somewhat elevated. The hair growth on the scalp was not equally dense everywhere. There were only a few teeth present.

SUMMARY AND CONCLUSIONS

Three patients with incontinentia pigmenti, a relatively rare pigmentary anomaly, are presented.

The disease is characterized by a bizarre distribution of the lesions, occurs early after birth, is almost exclusively limited to the female sex, has a distinctive histopathological picture and shows a tendency to spontaneous disappearance after many years. The condition is considered to be inflammatory in origin and the damage to the basal cells thus produced leads to "incontinence" or dropping down of the pigment into the corium where it forms deposits of melanin in the chromatophores.

Additional distinguishing features and findings are presented and the most striking points of our cases as well as those previously described are discussed.

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SELENIUM AND DENTAL CARIES

An Investigation Among School Children of Oregon

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THE possibility that trace elements may play an important role on the degree of susceptibility to dental caries has been indicated by the results of the epidemiological studies conducted by Dean and his associates.[1] These investigators have shown clearly the existence of an inverse relationship between minute amounts of fluorides occurring naturally in public water supplies and the incidence of caries in children. However, with the exception of fluorine, the possible effects of other trace elements, inhibitory or conducive, as an explanation for the variability in caries experience observed among different population groups have not been given enough consideration by research workers.

The purpose of the present study was an attempt to investigate the possible relationship between minute amounts of the trace element selenium and the wide variations in the degree of susceptibility to caries observed in two groups of school children residing in Oregon. The literature dealing with the trace element selenium contains some pertinent information, mentioned below, which prompted us to undertake this preliminary investigation.

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Dr. LeMar F. Remmert, associate chemist, Department of Agricultural Chemistry, made all the analyses for urinary selenium.

BACKGROUND OF THE INVESTIGATION

In the last few years, we have conducted a number of epidemiological studies on dental caries among school children living in various geographic regions of Oregon.[2-7] In general, our studies revealed that the children residing west of the Cascade Range showed high rates of caries experience and those east of the mountains low rates. The fluoride content of the public water supplies, availability of dental services, and quantity of candy bars and carbonated beverages consumed by the children were not found responsible for the wide variations in the rates of caries attack observed among the subjects. The only significant factor found was the existence of an inverse relationship between the prevalence of caries and the amount of sunshine available. In this connection, a further study is being planned for a better understanding of the sunshine-dental caries relationship. This study will be concerned with measuring photoelectrically the biologically effective component of the ultraviolet radiation of sunshine available in two regions of Oregon, one with low and the other with high caries prevalence rates. However, since a number of factors, either singly or in combination, may have a bearing on the degree of susceptibility to dental caries, an

attempt was made in the present study to ascertain the possible relationship between minute amounts of selenium and the incidence of caries in groups of school children born and reared in two geographic regions of Oregon.

Selenium has attracted the interest of research workers since it was discovered to be the cause of a serious and often times fatal disease in livestock which is known as "alkali disease" or selenium poisoning. As a result of extensive investigations, it is believed today that selenium is a normal constituent of soil and that its concentration depends upon the geological origin of the different soils. In the western states of the country, seleniferous soils have been identified in different regions. In Oregon only one seleniferous area in Malheur county of eastern Oregon has been reported.[8]

Although selenium poisoning in livestock has been studied extensively, detailed investigations of the effects of selenium intoxication on population groups have been few. In recent years, Smith and his collaborators[9, 10] conducted two field surveys for the purpose of ascertaining the effects of selenium on people living in known seleniferous areas. In an effort to discover symptoms characteristic of selenium poisoning, members of the families studied were given a physical examination and urine specimens were collected for determination of the selenium content. The results of these investigations revealed that a great percentage of the urine specimens contained selenium in various amounts. It was also found that one of the most pronounced symptoms of disease observed among the families examined was "bad teeth, varying from marked discoloration through all stages of decay."[9]

Whether or not the high incidence of dental caries as well as any of the other most frequently observed symptoms of disease could be considered as specific characteristics of selenium intoxication in man, could not be stated decisively. However, the investigators felt that at least some of the signs of ill health observed were related in some way to the ingestion over a long period of time of small amounts of selenium.

Outside of the known seleniferous areas, the hazards of selenium intoxication to man have not been studied extensively. Although not much is known about the selenium intake that may be tolerated without ill effects, the possible dangers to health from the cumulative effects of daily ingestion of minute amounts of selenium have been recognized. Selenium is known to be absorbed from the soil by all vegetation at least in minute amounts, and it is present in detectable amounts in all wheats.[11] Samples of wheat products analyzed in a city far removed from any seleniferous area were found to contain amounts of selenium ranging from 0.26 to 0.39 p.p.m.[12] Urine specimens collected from people in two cities who had no industrial or any other exposure to selenium were found to contain minute amounts of selenium.[11, 12] The use of insecticides containing selenium compounds has been recognized also as a possible public health hazard.[13, 14]

The possible relation between the trace element selenium and the condition of the teeth has received little attention. As it was previously mentioned, Smith and his collaborators observed high incidence of dental caries in people living in seleniferous areas,

although this symptom of ill health could not be decisively considered as a specific characteristic of selenium poisoning in man.[9, 10] Hance[15] reported that teeth collected in Honolulu were analyzed and found to be free of selenium. On the other hand, Williams and his co-workers[11] stated that in a sample of 100 grams of teeth collected in Washington, D. C., 0.005 mg. of selenium was found. English[16] noted certain structural changes in the dentition and jaws of dogs treated with two goitrogenic compounds, thiouracil and selenium. Wheateroft and co-workers[17] observed trends toward an increase of caries incidence in a group of white rats receiving intraperitoneally 1 mg. of selenium per kilogram of body weight as a daily dose.

METHODS AND FINDINGS

The subjects of the present study were white male high-school children who had been born and reared in the counties of Clatsop and Klamath. The reason for selecting subjects from these two counties of the state of Oregon was that in our epidemiological studies on dental caries, we found that the children of Clatsop country showed the highest rates of caries experience (14.4 D.M.F. teeth)* and those of Klamath county the lowest rates of caries experience (9.0 D.M.F. teeth).[2]

Altogether, fifty-three native born and reared school children served as subjects in the present study. Of those, twenty-four were attending the high school of Astoria, county seat of Clatsop county, and twenty-nine were attending the high school of Klamath Falls, county seat of Klamath county. All the children who participated in this study were selected by the principals of their schools on the basis of reliability and cooperation.

Each student was given a Mason jar, one-half gallon capacity, with instructions to take it home and collect during the week-end urine for a twenty-four-hour period.* By experiments on laboratory animals, it has been shown that the excretion level of selenium in the urine has a definite relationship to the amount ingested.[18]

In the determination of selenium the method of Klein[19] was used, with minor modifications, for the wet digestions and for the distillations. After the digestion of each 200 ml. aliquot of urine, 50 ml. of water, 40 ml. of 48 per cent hydrobromic acid, and 0.5 ml. of bromine were added for the distillation. Sixty to 75 ml. of distillate were collected in the usual manner. Fifteen milliliters of 48 per cent hydrobromic acid were added to each distillate to insure adequate acidity in the subsequent precipitation of elemental selenium. The precipitated selenium was separated, dissolved, and reprecipitated according to the method of Smith and associates.[9] The final determinations were made in a Model 14 Coleman spectrophotometer with the nephelometer attachment. When 10 μg quantities of selenium were added to certain of the urine samples, subsequent determinations indicated an average recovery of 89.7 per cent of this element.

All of the urine specimens analyzed were found to contain selenium in varying amounts. The distribution of urinary selenium concentrations of the two groups of subjects is presented in Table I. It is apparent from these data that the school children residing

*D.M.F. denotes the number of teeth which are Decayed, Missing, Filled.

*Toluene was used as a preservative agent.

in Clatsop county showed higher values than those observed among the subjects living in Klamath county. The mean value of urinary selenium concentration for Clatsop county is 0.049 p.p.m. and that for Klamath county 0.037 p.p.m. The difference between the two mean values was tested for significance by the analysis of variance and it was found to be significant at the 5 per cent level (Table II).

This direct relationship between the selenium content of urine and the prevalence of caries is of particular interest, in view of the fact that in our epidemiological studies among the school children residing in Clatsop and Klamath counties of Oregon we found that the fluoride content of the public water supplies, availability of dental services, and quantity of candy bars and carbonated beverages consumed

TABLE I. DISTRIBUTION OF URINARY SELENIUM CONCENTRATION OF SUBJECTS IN CLATSOP AND KLAMATH COUNTIES OF OREGON

CLATSOP COUNTY		KLAMATH COUNTY	
SE P.P.M.	NUMBER OF SUBJECTS	SE P.P.M.	NUMBER OF SUBJECTS
0-0.009	1	0-0.009	1
0.010-0.019	1	0.010-0.019	6
0.020-0.029	3	0.020-0.029	4
0.030-0.039	4	0.030-0.039	3
0.040-0.049	2	0.040-0.049	9
0.050-0.059	4	0.050-0.059	3
0.060-0.069	4	0.060-0.069	2
0.070-0.079	4	0.070-0.079	0
0.080-0.089	0	0.080-0.089	1
0.090-0.099	1	0.090-0.099	0
Mean 0.049 p.p.m.		Mean 0.037 p.p.m.	

TABLE II. ANALYSIS OF VARIANCE

VARIATION DUE TO:	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F
Between counties	.001754	1	.0017537	4.14*
Within counties	.021591	51	.0004234	
Total	.023345	52		

*Significant at the 5 per cent level.

COMMENT

The findings of the present investigation indicate that there is a direct relationship between the degree of susceptibility to dental caries and the urinary selenium concentrations of the subjects. The school children born and reared in Clatsop county have shown high values of urinary selenium concentrations and also high rates of caries attack, whereas among the children of Klamath county the opposite is true.

were not the factors responsible for the wide difference in caries experience (5.4 D.M.F. teeth) observed among them.[4]

The results of our study suggest the possibility that the trace element selenium may render the teeth more susceptible to dental caries attack just as another trace element, fluorine, is known to provide a great deal of protection against dental caries. Obviously, the above suggested hypothesis on the relationship between the trace

element selenium and the degree of susceptibility to dental caries must be tested by further experimentation with laboratory animals as well as with human subjects. It would be particularly advisable to conduct further studies on the prevalence of dental caries among groups of school children living in know seleniferous areas of the United States.

SUMMARY

A study was conducted for the purpose of ascertaining the relationship between the trace element selenium and the degree of susceptibility to dental caries observed among native born and reared school children in the counties of Clatsop and Klamath of Oregon.

It was found that a direct relationship existed between the prevalence of dental caries on one hand and the urinary selenium concentrations of the subjects on the other.

The results of this investigation suggest the possibility that, in an as yet unknown manner, the trace element selenium may render the teeth more susceptible to caries attack. Further studies are necessary for a better understanding of the selenium-dental caries relationship.

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THE GASTRIC RESPONSE OF NORMAL CHILDREN TO URECHOLINE

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DUODENAL intubation for diagnostic purpose of patients in the pediatric age group with symptoms referable to the upper gastrointestinal system has proved a valuable procedure. Intubation is sometimes difficult though usually successful in the hands of experienced workers. Various types of equipment have been studied in an effort to reduce the percentage of failures.[1, 2] There have been no reports on the value of cholinergic drugs as an aid in the passage of the tube through the pylorus.

The cholinergic group of drugs stimulate the parasympathetic nerves, and one of the results of such action is an increase in gastric peristalsis.[3] One of the safest and most effective of those used in man is Urecholine (urethane of β-methylcholine chloride), which has been employed effectively for gastric hypotonus and hypoperistalsis in adults who have had vagotomies for peptic ulcer.[4, 5] Because of the effect of Urecholine on gastric peristalsis it occurred to us that this drug might have some value in facilitating the passage of a tube through the pylorus in children who prove difficult to intubate. However, it seemed worth while to first make certain preliminary studies of the effect of the drug on salivary and gastric secretion of normal children. Also, such a study would allow an opportunity to observe any toxic effects of the type seen with similar drugs used in the treatment of patients with congenital megacolon.[6-10] This paper reports on observations of thirty-nine children on the pediatric ward of the Philadelphia General Hospital who were given Urecholine parentally.

SUBJECTS

The children, whose age range was from 2½ to 12 years, were convalescent from various diseases unrelated to the gastrointestinal tract. Care was taken not to include any subjects who had a history of allergy of any nature. All of the children were active and in good condition at the time of the procedure. No sedatives were given, but the pediatric resident who was to conduct the experiments made a special effort to prepare the child for the procedure from the psychological standpoint. If the child proved very difficult to manage during the study and failed to cooperate satisfactorily, the procedure was terminated, and attempted again on another day. Breakfast was withheld on the day of the test, but water was allowed during the night preceding the study. About 9 A.M. a No. 10 plain tip gastric tube was lubricated with a very small amount of petrola-

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tum and passed into the stomach via the nasal route, the length used being determined by the distance between the crown and xyphoid tip with three inches added. This was calculated to allow an adequate length of tube in the stomach to insure maximum drainage of the gastric contents. A fasting sample of gastric juice was aspirated with a 10 c.c. syringe, transferred to the test tube and marked. Subsequent samples were collected every fifteen minutes for a total of nine samples. Each sample consisted of all the juice that could be collected by a single aspiration. Immediately after the fourth sample was collected, Urecholine* was given subcutaneously in the deltoid area, 5 mg. for children 5 to 7 years of age, and 7 mg. for children 8 to 12 years of age, inclusive. The subjects were urged to report any symptoms experienced. They were constantly coaxed to expectorate all of their saliva during the study. Aspiration of saliva was achieved by a suction device to which was connected a dental mouth suction piece. As a further precaution against saliva entering the stomach cotton tampons were packed beside the opening of Stenson's duct, and changed as they became saturated with saliva. All of the gastric samples were analyzed separately and all analyses were made within ten minutes of the collection. The physicians who conducted the experiment analyzed the samples. Blood pressure and pulse determinations were made at least every half hour, and notes kept of the presence of abdominal cramps, nausea, desire to urinate or defecate, sweating, flushing, salivation, and of pulmonary constriction. Atropine sulfate was available to administer as an antidote, if necessary.

Unless a patient exhibited at least sweating, salivation, and abdominal discomfort after Urecholine, the procedure was terminated. In a subsequent study on another day an additional milligram over the original dose was used. The children were allowed to resume their normal ward routine within one-half hour after the procedure ended.

BASIC DATA

These consist of 351 gastric samples from thirty-nine patients and eighty-eight samples of saliva from eleven patients.

LABORATORY METHODS

The values for acidity on the gastric samples were obtained from the Toffer quantitative method using dimethylaminoazobenzene for free hydrochloric acid and phenolphthalein for total acidity. The values are reported in milliequivalents per liter which are identical with "units" or "degrees" in the older system of notation.

RESULTS

There were nine subjects who were uncooperative and swallowed most of their saliva during the test. The results of the acidity level determinations in a sample from this group of subjects are shown in Sample Chart I. The mean for the amount of gastric juice collected before Urecholine was given was 18.3 c.c., while the mean for the samples taken after Urecholine was 13.2 c.c.

The range of free hydrochloric acid before Urecholine was 0 to 58 meq.

*The Urecholine used in this study was kindly supplied by the Merck Co., Rahway, N. J.

per liter, with a mean of 11.2 meq. per liter, and the range of total acidity before Urecholine was 0 to 65 meq. per liter, with a mean of 20.1 meq. per liter. The range of free hydrochloric acid after Urecholine was 0 to 26 meq. per liter, with a mean of 0.94 meq. per liter, while the range of the total acidity was 0 to 36 meq. per liter with a mean of 8.1 meq. per liter.

SAMPLE CHART I

FROM RESULTS IN NINE PATIENTS WHO SWALLOWED SALIVA

S. S., AGED 10 YEARS

TIME (HR.)	AMOUNT (C.C.)	MEQ./L.	
		HCl	TOTAL ACIDITY
Fasting	7	0	6.0
¼	6	21.0	35.5
½	6	18.5	34.5
¾	4	13.5	24.5
1*	12	25.0	36.0
1¼	15	0	3.0
1½	18	0	1.0
1¾	7	0	2.0
2	10	0	3.0

*Urecholine given immediately after 1-hour sample was aspirated.

SAMPLE CHART II

FROM RESULTS IN THIRTY PATIENTS WHO COOPERATED SATISFACTORILY

R. W., AGED 8 YEARS

TIME (HR.)	AMOUNT (C.C.)	MEQ./L.	
		HCl	TOTAL ACIDITY
Fasting	35	8.5	19.5
¼	7	5.0	16.0
½	4	0	5.5
¾	4	0	10.5
1*	21	31.5	40.0
1¼	22	64.0	73.0
1½	21	69.0	77.5
1¾	9	77.5	89.0
2	1	68.0	84.5

*Urecholine given immediately after 1-hour sample was aspirated.

There were thirty patients who cooperated satisfactorily and expectorated their saliva, or in whom suction and the use of cotton tampons were employed to prevent saliva from entering the stomach (Sample Chart II). The range of free hydrochloric acid before Urecholine was given to this group of patients was 0 to 85 meq. per liter, with a mean of 20.2 meq. per liter, and after the drug the range of free hydrochloric acid was 0 to 99 meq. per liter with a mean of 36.1 meq. per liter. The figures for total acid levels show a range of 1.5 to 95 meq. per liter, with a mean of 30 meq. per liter before the drug and a range of 0 to 112 meq. per liter after it, with a mean of 48.5 meq. per liter.

The amount of saliva was measured before and after the administration of Urecholine in eleven of the thirty patients in whom suction was used. There was an average increase in the total sample after Urecholine of 70.8 c.c. of saliva.

COMMENTS

In the experimental animal certain choline derivatives have been shown to produce physiologic results similar to those that follow stimulation of the parasympathetic nerves.[3, 11] These results consist of peripheral vasodilatation, tachycardia, increased bladder tone, bronchioconstriction, sweating, and salivation. Starr has demonstrated these signs and symptoms in healthy adults given cholinergic drugs.[12]

Acetylcholine, the first of the choline series to be discovered, has proved to be of little therapeutic value because of the rapidity with which it is destroyed in the body and because of its nicotine-like action.[13] However, there are three other drugs of the cholinergic group that have been favorably reported on; namely, acetyl-β-methylcholine (Mecholyl), carbam-

inoylcholine (Doryl) and β-methylcholine urethane (Urecholine).

Mecholyl lacks the nicotine-like action of and is more stable in the body than acetylcholine.[11] According to Starr the oral dose of this drug is ten to thirty times the subcutaneous dose.[14] Doryl, which was the first stable choline derivative synthesized, is a potent drug, and because of its strong nicotine-like action is dangerous.[15] Both Mecholyl and Doryl have been favorably reported on in the medical management of congenital megacolon.[6-10] However, because of the element of danger with the use of Doryl and since the surgical management of this condition has improved so much,[17] it would seem unwise to give this drug to a child. There has been a recent report of the death of an infant attributed to this drug.[18] Careful studies on the experimental use of Urecholine in healthy adult volunteers and in adults who have had a vagotomy for peptic ulcer establishes this drug as the safest and most satisfactory generally in the cholinergic group.[1-5, 14]

The figures on the acid levels in the nine patients who failed to cooperate satisfactorily and swallowed almost all of their saliva indicate the importance of the neutralizing effect of saliva on gastric acidity. Thus, the mean for free hydrochloric acid determinations before Urecholine was given was 11.2 meq. per liter and after the drug was only 0.94 meq. per liter. There were two patients in whom no free hydrochloric acid was demonstrated and a third in whom free hydrochloric acid was present in only one sample. In the other six patients there were twenty-two samples collected after Urecholine in which no free hydrochloric acid was found. Of the samples taken before Urecholine was given, there were only six specimens that had no free hydrochloric acid. It would appear that any increase in gastric acidity that results from stimulation by cholinergic drugs can be compensated for by the neutralizing effect of the increased secretion of saliva when swallowed.

In the thirty patients in whom a minimum amount of saliva was allowed to enter the stomach, there was a definite but not marked increase in acidity in twenty-seven of the thirty patients following the administration of Urecholine (Sample Chart II). Wolman[16] states that if all influences due to age and individual variation are ignored, the data for the child's fasting gastric juice at any single moment show a free acidity range of 0 to 100 meq. per liter. There was no typical pattern for the increase, but the maximum rise of free and total acidity occurred on an average of 39.33 thirty-eight minutes after the drug was given and coincided with the peak of intensity of symptoms.

The salivary response was fairly marked in all of the children. The amount of saliva collected was measured in eleven subjects. There was a mean increase of 70.8 in the total sample collected subsequent to the administration of Urecholine. The results again emphasize the importance of preventing saliva, with its neutralizing effects, from entering the stomach during a study of this type. By the same token, when Urecholine is given to a child, the increased salivary flow should adequately balance the increase in acid concentration in the stomach. Further study of the effect of the cholinergic drugs on pan-

creatic enzymes should prove interesting.

No subjects were included in the study who did not have two or more symptoms of parasympathetic nerve stimulation previously discussed. All of the children complained of abdominal cramps and considerable nausea. We were quite impressed with the emotional reaction of the children. They were apprehensive, restless, and difficult to control following the administration of the drug. Most of them complained constantly of the drug's effect on them. None of the children seemed ill enough to need an antidote (atropine sulfate) and all were free of any symptoms within one-half hour following completion of the test.

CONCLUSIONS AND SUMMARY

Thirty-nine normal children, free from any symptoms referable to the gastrointestinal tract, were given Urecholine subcutaneously.

Studies of the salivary secretion, free and total gastric acidity, and the general systemic effects produced by the drug were made.

There was a marked increase in both free and total acid levels in the stomach of twenty-seven of the thirty patients following the administration of the drug. In three patients there was no increase in the acid levels.

All of the children exhibited signs and symptoms of parasympathetic stimulation due to the drug. They all objected strongly to the effects of the drug, especially the abdominal cramps, apprehension, and nervousness, and were rather difficult to manage for the procedure.

The systemic reactions to the Urecholine in therapeutic dosage are so strong that this drug seems unsuitable for use in facilitating the passage of a tube through the pylorus during duodenal intubation.

We are deeply grateful to Drs. Isaac Starr and Thomas E. Machella for their valuable suggestions in planning this study.

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VARIATIONS IN BLOOD PRESSURE IN HOSPITALIZED CHILDREN

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NUMEROUS studies have been made to determine the normal blood pressure of children of various ages,[1, 2, 3, 4, 5] and it is known that the pressure is influenced by respiration, coughing, straining, eating, emotions, and other factors. However, we are unable to find any serial quantitative evaluations of blood pressure in children under conditions of hospitalization. We have thought that such studies would be of value in ascertaining to what extent factors other than disease processes themselves may produce fluctuations of blood pressure. For example, what relationship exists between blood pressure values obtained in the admitting room as compared to those after the child has been transferred to the ward? Furthermore, what significance can be attached to slight hypertension on admission in a child who has a disease ordinarily unrelated to hypertension? Finally, to what extent do ordinary hospital conditions influence blood pressure? It is apparent how such information would be of value in the interpretation of a child with acute nephritis and moderate hypertension. How much of his elevation of blood pressure might be due to fright or emotional tension alone? The present paper represents an attempt to answer, to some degree, these practical questions.

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This work was supported by a grant from the United States Public Health Service.

METHODS

Most of the patients in the study were admitted for elective surgical procedures and mild infections, and none for diseases ordinarily associated with hypertension. A few children were moderately ill. There was a rather even distribution of patients between the ages of 2 and 12 years. There were 729 arm blood pressure determinations carried out on ninety-six children in the study. From four to as many as thirty-nine, with an average of eight, recordings were made.

In thirty-six cases, initial blood pressure determinations were made while the patient was in the admitting room, and in sixty cases the initial pressure was obtained after the patient was on the ward, ranging from a few minutes after admission to a day or more. In both groups of patients determinations were made at intervals thereafter.

On each patient, the following factors were evaluated at the time of every blood pressure determination: (1) diagnosis and degree of illness; (2) environmental circumstances in admitting room or ward (presence or absence of parents, visits of parents, painful procedures, crying of other children, degree of activity, and apparent emotional adjustment of the child); (3) whether the child was awake or asleep; (4) whether or not he was crying; (5) pulse rate; (6) time of day; and (7) whether or not the blood pressure recording was con

sidered to be reliable, so that it could be discarded if not.

In all instances, a Baumanometer sphygmomanometer was used and a blood pressure cuff 9 cm. in width, since all of the children studied were over 2 years of age. Robinow and associates[6] showed that when a 9 cm. cuff is used in children 1 to 13 years of age there is close agreement in pressures obtained by a sphygmomanometer and direct intra-arterial determinations.

Although there were several persons who recorded the blood pressures of the children in the group studied, all pressures on any one child were determined by the same individual. Systolic and diastolic pressures were obtained at each determination.

RESULTS AND DISCUSSION

I. *Effects of Admission to Hospital.*—It is a common observation that children admitted to the hospital are frequently nervous, apprehensive, and crying. Strangeness of surroundings and knowledge that separation from parents is imminent are probably the two chief causes of such emotional tension. To what extent is this reflected in differences between blood pressures on admission and those later on the ward?

In order to investigate this point, serial blood pressure determinations were obtained on thirty-six children at the time of appearance in the admitting room, and afterward on the ward. Three patterns of response were noted, as follows:

1. *Blood Pressure Higher in Admitting Room Than Subsequently on Ward in First Twenty-four Hours:* This was the most common pattern observed, since 53 per cent of these patients showed this response. Our interpretation is that apprehension and fright over examination and admission to the new surroundings of a hospital produced initial elevation, and that fall to a more stable level resulted from adaptation to ward conditions. Such a fall usually occurred within the first two to four hours, but varied greatly. Fig. 1 shows the distribution of the patients in regard to this factor and the extent of pressure differences. Fig. 2 illustrates a typical response of this nature.

2. *Blood Pressure Higher on Ward in First Twenty-four Hours Than in Admitting Room:* In 30 per cent of cases the blood pressure became noticeably higher after the child had been transferred to the ward than it had been in the admitting room. Such rises commonly occurred in the first six hours. We attribute this chiefly to separation from parents and newness of surroundings. Fig. 3 shows the distribution of patients who made this type of response and the extent of pressure changes. Fig. 4 illustrates a typical response of this nature. It will be noted that although a systolic difference of 30 mm. Hg occurred in this case, the maximum systolic pressure was only 110 mm. Hg and the maximum diastolic pressure was 70 mm. Hg. While this is not hypertension it does show the great variability of individual children in regard to blood pressure.

3. *No Appreciable Changes in Blood Pressure Associated With Admission:* Variations of pressure 5 mm. Hg or less were not considered significant, inasmuch as they are within the range of technical error. Of the thirty-six children, 17 per cent showed insignificant variations in pressure. Fig. 5

illustrates such a case. As a group, these individuals seemed more phlegmatic than those who revealed greater changes in pressure.

In general, the group of sixty children whose first blood pressure was recorded after they had made initial adjustments to ward conditions showed insignificant alterations.

In general, the greatest fluctuations occurred in systolic pressures, but diastolic pressures usually followed the systolic closely. If rises in systolic blood pressure occurred there were also rises in diastolic pressure but usually to a less degree. The same was true of falls in pressure. On several occasions the greatest variation

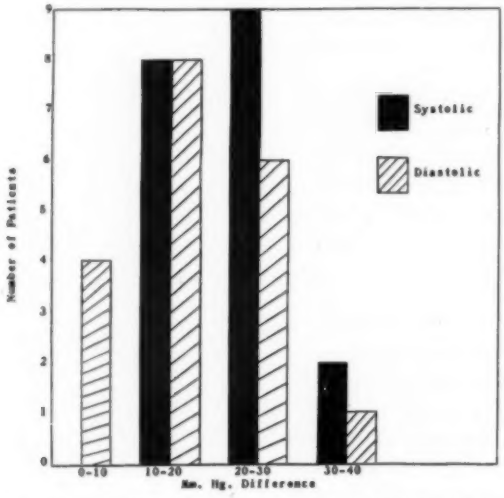

Fig. 1.—Extent of maximum fall in blood pressure from admission to end of first twenty-four hours.

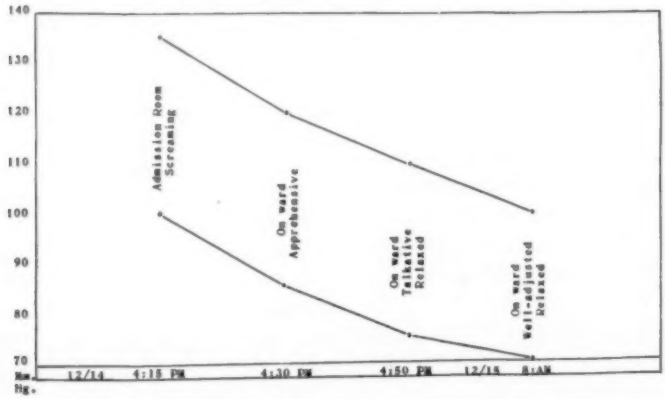

Fig. 2.—Chart illustrating blood pressure in Admission Room higher than on ward after adjustment to hospitalization. This was most common response noted. Patient aged 6½ years.

occurred in the diastolic blood pressure, but in every instance the difference was usually very slight, never being more than 5 mm. Hg. Of the total number of blood pressures taken the diastolic pressure never varied as often, nor were the fluctuations as great, as the systolic.

II. *Other Factors Influencing Blood Pressure.*—Although early fluctuations in blood pressure after admission seemed clearly related to emotional tension caused by factors already discussed, other events also exerted an influence, but to a less degree. Some children were remarkably stable and showed practically no variations in pressure.

1. *Visits of Parents:* A frequent observation was that the blood pres-

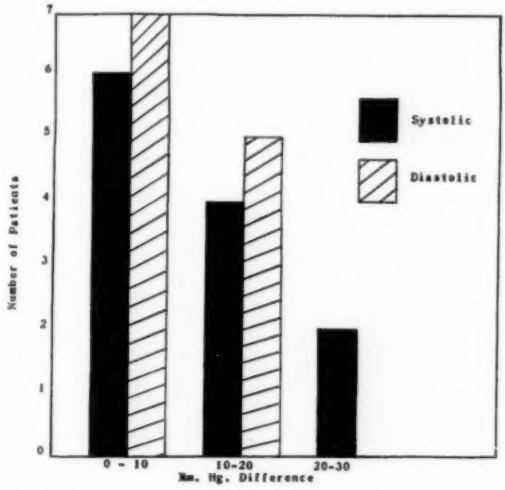

Fig. 3.—Extent of maximum rise in blood pressure from admission to end of first six hours.

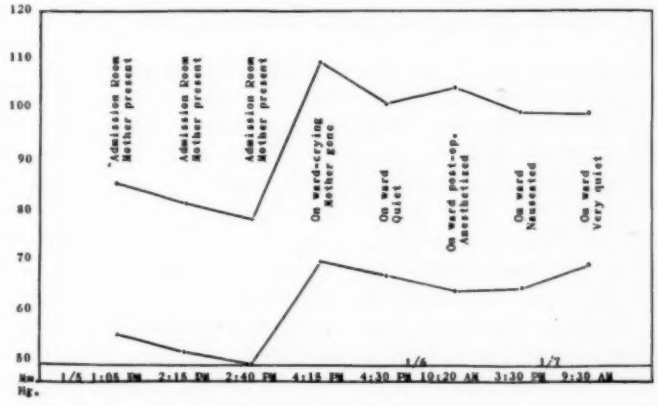

Fig. 4.—Chart illustrating rise of blood pressure after admission to ward presumably because of separation from mother and newness of surroundings. Second most common response noted. Patient aged 5 years.

sure of hospitalized children tended to rise slightly when their parents visited them. In some instances, the pressure rose when the parents were with the child on the ward, and in other cases this effect was most noticeable after the parents departed. We interpret the first rise to be due to increased motor activity usually associated with these visits and to some degree of excitement. The rise after departure of the parents seemed clearly related to emotional upset. The fluctuations in blood pressure associated with visits of parents rarely exceeded 10 mm. Hg systolic or diastolic. This is in contrast to the frequently large variations previously mentioned at time of initial separation from parents on admission.

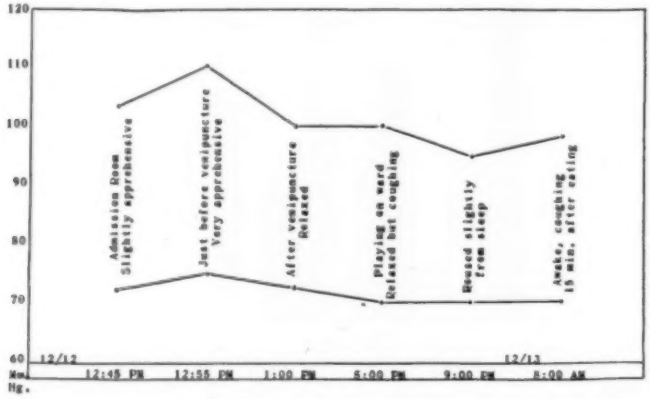

Fig. 5.—Chart illustrating insignificant alteration of blood pressure associated with hospitalization. This was least common response noted. Patient aged 9 years.

2. *Initial Blood Pressure Recording:* Some of the children had a slight rise in pressure apparently due solely to apprehension over the first blood pressure recording. It was difficult to interpret this, in view of the fact that frequently the child was already upset from other factors. As the children became used to having their pressures taken, and to the examiners, fewer fluctuations were seen.

3. *Physical Activity and Play Activity:* Physical activity and play on the ward, or in the recreation room, was often associated with slight to moderate elevation of pressure. Motor activity and the excitement of play were thought to be responsible. In a few instances, a visit to the playroom was associated with a slight decrease in pressure. In such cases the pleasant surroundings may have accelerated the emotional adjustment of the child and relieved tension. Since we did not measure closely the degree of physical activity, or estimate the probable extent of excitement of playroom recreation, we can only speak in general terms.

4. *Effect of Awakening:* Blood pressure determinations made while the child was asleep and immediately after he awakened sometimes showed a sharp but slight elevation.

5. *Effect of Meals:* Meals exerted practically no effect on blood pressure in this study, although in a few in-

stances there was a slight elevation immediately after eating.

6. *Noise on Ward:* The usual bedlam that sometimes occurs on any pediatric ward seemed to have little or no influence on the blood pressure of children who were, themselves, lying quietly in bed. Specifically, we were surprised to find that in no instance could we relate a rise in pressure to the crying of other children on the ward, regardless of the age of the child studied. This seems strange in view of the known fact that children do become emotionally upset when they observe other distraught children.

7. *Effect of Painful Procedures:* Slight rises in blood pressure were often noted in association with painful procedures, such as obtaining samples of blood. In patients studied before and after surgical procedures (circumcision in older children or adenoidectomy and tonsillectomy) postoperative rise in blood pressure often occurred, but never exceeded 15 mm. Hg systolic or 10 mm. Hg diastolic. A combination of factors undoubtedly accounted for these elevations, with prominent roles being played by pain, fright, and separation from parents. However, a minority of children so studied failed to have any elevation.

8. *Effects of Illness:* In children who were ill from conditions not ordinarily associated with changes in blood pressure there was a noticeably stable pattern of the pressure recordings, with the more acutely ill children fluctuating less than those mildly ill. We believe this to be due to dulling of the sensorium associated with illness which prevented factors discussed above from influencing pressure.

9. *Anger:* It is so well known that anger raises blood pressure that it seems superfluous to mention that it was noted as a cause of elevation of blood pressure.

10. *Age:* Surprisingly enough, we were unable to note any effect of age of the child on fluctuations in blood pressure, as related to any of the factors discussed above. One would expect that younger children, who are apparently more emotionally upset under conditions of hospitalization, would show greater changes in pressure.

SUMMARY AND CONCLUSIONS

1. In ninety-six children admitted to the hospital 729 determinations of blood pressure were obtained.

2. An effort was made to correlate fluctuations in blood pressure with various factors, such as separation from parents, activity, recreation, painful procedures, degree of illness, eating, awakening, and various emotional factors.

3. The chief fact noted was that children varied greatly in regard to whether their blood pressure fluctuated or remained relatively stable.

4. Three patterns of response were recognized in respect to initial pressure adjustments. The most common course was for the pressure to be higher in the admitting room and then to become progressively lower on the ward. The next most common course was the pressure to rise on the ward in the initial hours after admission and then to become progressively lower. The third pattern was less frequent, and consisted of relatively little fluctuation.

5. Emotional tension incident to admission to the strange surrounding of a hospital, and anticipation of actual separation from parents seemed to be the factors which influenced

pressure the most. When the stabilized pressure was compared to the highest pressure in the initial hours of admission and hospitalization, differences as great as 30 to 40 mm. Hg were encountered in some patients.

6. Other factors causing variations in blood pressure were: physical activity and recreation, painful procedures and the postoperative state, visits of parents, eating, awakening, and anger. In no instance were these variations as great as those encountered in the initial hours after admission.

7. Acutely ill children seemed to have a more stable blood pressure pattern than those not ill or only mildly so.

8. This study shows that in the interpretation of blood pressure in hospitalized children careful attention must be given to emotional and environmental factors, and that serial, rather than single, determinations are necessary in order to ascertain the truly stabilized pressure.

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THE TREATMENT OF PINWORM INFECTION (ENTEROBIUS VERMICULARIS) WITH EGRESSIN

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THE pinworm *Enterobius vermicularis* is the most common helminth in the United States. Because of its simple life cycle it is a difficult parasite to eradicate from man. Numerous methods of therapy have been tried, including drugs, ointments, enemas, mechanical measures, and hygienic control. None of these measures has been entirely successful. The ointments seem to help by relieving the pruritus; none of the jellies or suppositories has been uniformly effective in killing either the worms or their eggs; mechanical measures are essential in conjunction with medical treatment but are of little value alone in children[1] although infection in adults may be eliminated by good personal hygiene.[2] Enemas alone have shown some promise if given repeatedly over a sufficient time, particularly hexylresorcinol enemas, but even they are much more effective in conjunction with oral hexylresorcinol.[3] Of the better known anthelminthics used in the treatment of pinworms, gentian violet is the most effective.[4] Tetrachlorethylene is probably the most effective single dose treatment.[5] Lubisan,[6] hexylresorcinol,[3] Diphenan,[7] phenothiazine,[8] and less known agents are not ideal because of their relative ineffectiveness, toxicity, or impracticability.

Recent studies by Wells and associates[9] indicate that terramycin is effective against pinworms in man. Wells' extensive studies on the effect of a number of antibiotics against the pinworm Aspiculuris in mice indicate that both terramycin and aureomycin are effective.[10] Our studies using bacitracin against mouse infections with Aspiculuris and Syphacia indicate that this antibiotic is effective. We treated fifteen pinworm-infected persons with bacitracin and, on the basis of only two Scotch tape swabs taken seven to fourteen days after treatment, 40 per cent had lost their worms. We gave 120,000 units of bacitracin daily for fourteen days to adults. The daily dosage for children was 1,000 units per pound of weight.

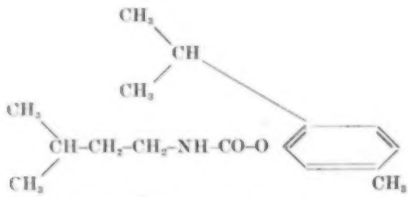
Recently, Eicholtz and co-workers[11] reported that Egressin, a new chemotherapeutic agent, is effective against pinworm. Egressin is a thymol compound (see accompanying formula).

Egressin was first synthesized at the Pharmacological Institute of the University of Heidelberg, and came to the attention of our chemists in their postwar missions in Germany.

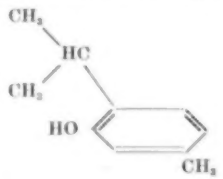
From the Babies Hospital, and the Department of Pediatrics and The School of Public Health of Columbia-Presbyterian Medical Center.

The authors wish to thank Sharp & Dohme, Inc., for the Egressin used in this study.

It is a colorless, crystalline material with a slight thymol odor, is soluble in organic solvents, but almost insoluble in water (less than 1:50,000), and has a melting point of 57° C. It is poorly absorbed from the gastrointestinal tract, although its absorption is somewhat increased when administered in an oleaginous vehicle. In chronic toxicity studies in dogs, neither the drug itself nor its split product (thymol) appeared in the urine, although crystals of the drug are found in their feces. The urine of human beings receiving the drug has shown no phenol bodies and it is believed that the low toxicity of the drug is due to its slight absorption from the gastrointestinal tract, which would explain the lack of any signs of thymol intoxication. Eicholtz and associates treated hospitalized and clinic patients, including both children and adults, and found that 90 per cent remained NIH (National Institute of Health) swab negative for a period of three to six weeks following a two-day course of therapy, 57 per cent remained NIH swab negative for a period of four months following therapy, 34 per cent showed recurrence of eggs within four to six weeks of therapy, and 5 to 10 per cent failed to respond to Egressin treatment, even after repeated courses of the treatment with the drug. Toxic manifestations included sleeplessness in children, slight diarrhea in some adults, and nausea and vomiting in heavy smokers or those consuming strong alcoholic beverages or a high fat diet.



Egressin (N-isoamylcarbaminic acid-3-methyl-6-isopropyl-ester)



Thymol

METHODS

The individuals treated by us with Egressin ranged in age from 1 to 50 years. The diagnosis was made by means of NIH Cellophane swab. Three swabs were taken on consecutive days, on arising, prior to treatment, and three to six swabs were taken in the morning seven to twenty-eight days after treatment. Except for the hospitalized patients, whose swabs were taken by the staff, all swabs were taken by an adult member of the family and they were all examined in the parasitology laboratory.

Egressin was administered for two days, a total of six doses as recom-

mended by Eicholtz and associates. Children (aged 1 to 10 years) were given 1 Gm. after each meal. Older children and adults received 2 Gm. after each meal. For children who were unable to swallow them, the tablets were crushed and mixed with applesauce. No deleterious effects were noted in these patients and the effectiveness of the drug did not seem to be diminished. The tablets should not be chewed as Egressin causes a mild irritation of the buccal mucosa. During treatment and one day before and after treatment no fatty or fat-prepared foods were eaten, no alcoholic or carbonated beverages were consumed, and smoking was discontinued. These measures were in effect for the four-day period. On the fourth day a magnesium sulfate purge was administered. Most of the patients were treated at home and we had to rely on the patient taking the drug as recommended. It was suggested to the patients that the following hygienic measures be routine during the course of treatment: (a) scrubbing the hands and fingernails with soap and a brush after each defecation and before each meal, (b) washing the anal region with a piece of cloth dipped in soapy water in the morning and evening, and after each defecation, (c) wearing close fitting cotton pants day and night and boiling them when changed; boiling bed linen twice weekly, and (d) vacuum cleaning the bedroom and bathroom, and dusting toys with a moist piece of cloth daily.

RESULTS

Twenty-eight children and fifteen adults were treated with Egressin and at intervals following treatment NIH swab examinations were made with the results shown in Table I. Thirty-nine per cent of the children and 47 per cent of the adults were found to be negative on the basis of from three to six NIH swab examinations seven to twenty-eight days after treatment. The poorer response of children to the Egressin therapy may be due to their heavier infections and also to the difficulty of hygienic control of the younger group and possible reinfection.

TABLE I. RESULTS OF TREATMENT OF ENTEROBIUS INFECTIONS WITH EGRESSIN BASED UPON NEGATIVE NIH SWABS AFTER TREATMENT

AGE YEARS	NUMBER TREATED	NUMBER NEGATIVE 7-28 DAYS AFTER TREATMENT	PER CENT NEGATIVE
1 to 13	28	11	39
Adults	15	7	47
Total	43	18	42

The cure rate was 42 per cent for the two groups combined. By cure, we mean that all NIH swabs taken seven to twenty-eight days after treatment were negative for Enterobius eggs. Sawitz and collaborators[12] have demonstrated that a single NIH swab examination detects approximately 70 per cent of the infections present and seven swabs disclose 99 per cent of them. It is obvious, therefore, that our figures of cure rate are somewhat high, inasmuch as only three to six swab examinations were made after treatment on each patient. It is ex-

tremely difficult and even impossible to secure as many as seven daily NIH swabs from clinic and private patients who are not hospitalized. Correcting the observed 42 per cent cure rate according to the Sawitz data the probable cure rate is approximately 38 per cent. Ten of the patients who still harbored pinworms after the first treatment were given a second two-day course of Egressin, following which six were negative.

Undesirable side effects of the treatment included vague abdominal distress in two boys of the same family; physical examination was negative. Full recovery followed bed rest within six to ten hours after completion of therapy. The mother of these two boys was taking elixir of terpin hydrate cough syrup throughout her course of Egressin therapy and started to smoke a cigaret after her last dose, whereupon she immediately felt light-headed, as though she were going to lose consciousness. In addition, she complained of vague abdominal cramps. Physical examination was negative, and all symptoms abated within six to ten hours. The most severe side reaction occurred in a woman who drank about one-third of a rye highball approximately eighteen hours after her last dose of Egressin. She had an immediate vasomotor flush of her face, head, and upper extremities, with pounding in the temporal regions of the head, and felt hot and feverish. Her reaction was described by her physician as one similar to anaphylactic shock. Physical examination was negative within minutes of her reaction, and on rest in bed for four to six hours her symptoms cleared up completely. No diarrhea, sleeplessness, nausea, or vomiting, such as reported by Eicholtz and associates, was noted.

Two patients who were treated in the hospital, with a long-term follow-up on the hospital wards, showed no significant changes in hemoglobin, red cells, urinalysis, sedimentation rate, or nonprotein nitrogen. One of these two boys was recovering from acute glomerulonephritis; the drug apparently had no deleterious effects on his recovery. The only significant laboratory change was a drop in the eosinophil count in both boys, from 17 to 5 per cent of the white blood cells in one and from 10 to 6 per cent in the other.

DISCUSSION

The cure rate of pinworm infections with Egressin in the dose employed is approximately 40 per cent; however, the treatment has the advantage of lasting only two days. It is not unlikely that an additional day or two of therapy would increase the cure rate. Repeated two-day courses at weekly intervals also are suggested in view of the favorable results of the second treatment of the group of ten patients. Although the cure rate from gentian violet therapy is approximately twice as high as that from Egressin, it must be taken over a ten-day period and, owing to minor toxicity, the complete course cannot always be given. The Egressin tablets are large but, in case a child cannot swallow them, they can be crushed and eaten with applesauce.

It is apparent from the toxic reactions reported that alcohol is contraindicated not only on the days of Egressin therapy, but also on the day before and day after treatment, but this is hardly a contraindication in children.

SUMMARY

1. Egressin therapy for pinworm infection is approximately 40 per cent effective when given for two days; children's dose 1 Gm. t.i.d., and adult's dose 2 Gm. t.i.d.

2. Alcohol, smoking, and fatty foods are contraindicated during treatment with Egressin.

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INTESTINAL OBSTRUCTION IN A PREMATURE INFANT TREATED BY RESECTION AND PRIMARY END-TO-END ANASTOMOSIS

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INTESTINAL obstruction is a surgical emergency for which one caring for infants must be constantly alert. As a suggestion of its frequency in the newborn period, one of us (C.W.B.) has observed eight cases of intestinal obstruction within the first two weeks of life among 8,000 live births at Bellevue Hospital, the New York Hospital, and Madigan Army Hospital.

Reported survival among infants with intestinal obstruction remains low. In Ladd's[1] series, published in 1943, of fifty-nine infants with extrinsic obstruction but 63 per cent survived, while of eighty-seven infants with intrinsic obstruction only 27 per cent survived. Glover and Barry[2] indicate progress in treatment of intestinal obstruction. Over-all survival among forty-four infants with all types of intestinal obstruction in three Cleveland hospitals from 1924 to 1948 was 43 per cent; survival increasing from 19 per cent between 1924 and 1938 to 65 per cent at University Hospital from 1944 to 1948.

The higher mortality among infants with intestinal obstruction results in part from other associated anomalies, but can be further reduced with further cooperation of surgeon and pediatrician. Early diagnosis, adequate preoperative preparation, and careful postoperative care are, of course, of prime importance for survival. The ideal bowel surgery for the infant remains controversial. A patient recently treated on the Pediatric and Surgical Services of Madigan Army Hospital demonstrates the success with which an end-to-end anastomosis may be employed in a small patient. We believe that she is one of the smallest infants on whom such surgery has been successfully performed.

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CASE REPORT

The patient was born one month prematurely at Madigan Army Hospital of a 19-year-old white mother following a pregnancy complicated by hydramnios. The infant's course is shown in Fig. 1. Though edematous at birth, the edema subsided by her fourth day of life with fluid restriction, and her weight fell to 4 pounds 12 ounces. Thereafter, she ate well, gained rapidly, and by her twelfth day of life reached a discharge weight of 5 pounds 7 ounces. Thirty-six hours after arriving home, she suddenly developed continuous projectile vomiting of yellow-green material, and became somnolent and listless, with wrinkled skin, scanty urination, and absent bowel movements. After thirty-six hours of symptoms her mother returned her to the hospital.

On readmission, the child appeared profoundly dehydrated and marasmic;

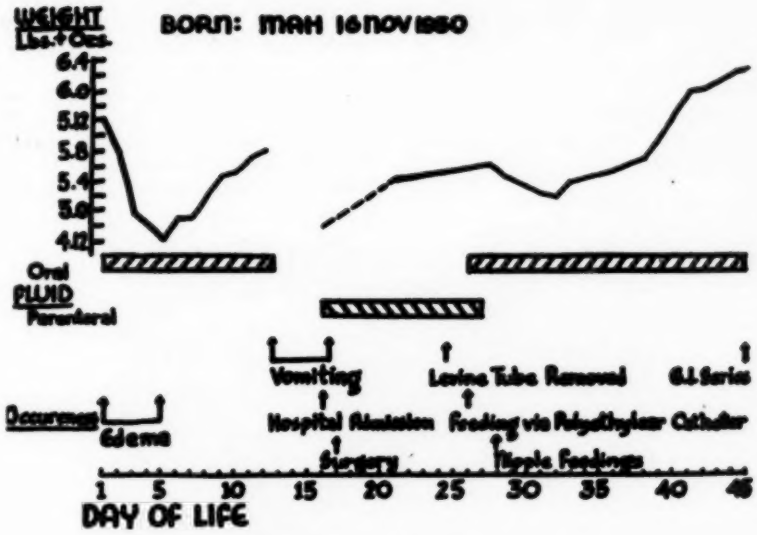

Fig. 1.—Patient's hospital course.

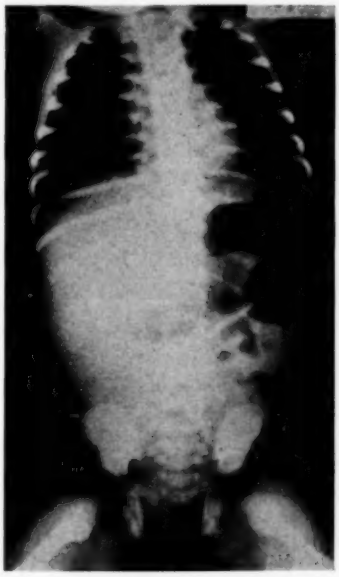

Fig. 2.—X-ray of abdomen. Film on entry shows dilated stomach and upper small bowel, with absence of air in colon and rectum, indicative of intestinal obstruction.

her skin was gray and stood up in folds, her fontanels sunken, lips dry and cracked, breathing acidotic; abdomen had large left upper quadrant waves moving to the right; and her weight was 4 pounds 14 ounces. Initial abdominal film (Fig. 2) showed dilated stomach and upper small bowel.

Fig. 3.

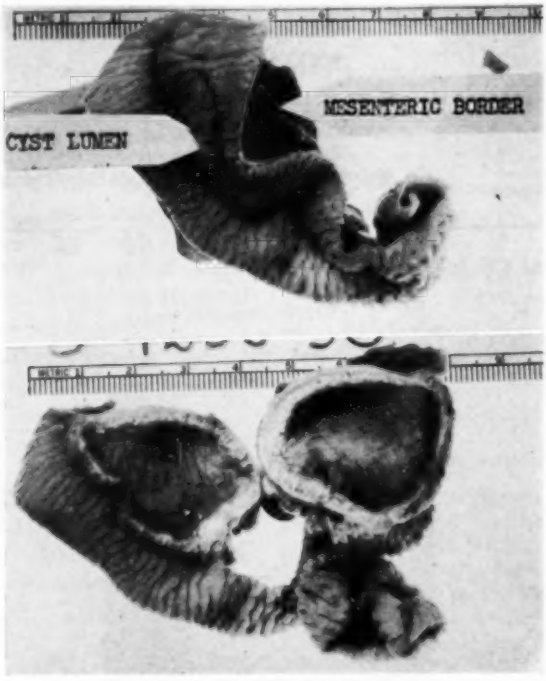

Fig. 4.

Fig. 3.—Photograph of specimen, showing section of ileum opened, and the duplication intact.

Fig. 4.—Photograph of specimen. Opened duplication demonstrates its common wall with, and opening into, the ileum.

Following twenty-four hours of parenteral hydration, her skin and fontanels resumed normal turgor, color improved markedly, and she seemed in optimal condition for surgery. A celiotomy was performed under local procaine anesthesia supplemented by open drop ether. On making a right paramedian incision at the level of the umbilicus, and opening the peritoneum, a clockwise volvulus of the small bowel became evident, twisted through four complete turns. On reducing it, a defect was found in mesenteric fixation, associated with a mass on the mesenteric border of the ileum which could not be separated from it. Ten centimeters of ileum were resected, and a primary end-to-end anastomosis carried out with a posterior row of 5-0 silk and a mucosal layer of continuous catgut sutures carried anteriorly as a Connell suture. The mesenteric defect was repaired, and the abdomen closed with interrupted silk sutures.

Figs. 3 and 4 show the specimen. Pathologically the lesion consisted of a 3.2 × 2.5 × 1.6 cm. rounded smooth-

walled hollow structure with the external appearance of small intestine and a common wall with the ileum. An oval 0.4 cm. × 0.2 cm. ostium connected its lumen with that of the ileum. Grossly and microscopically the mucosal lining and smooth muscle wall were similar to that of the adjoining small intestine.

Postoperatively, the child was maintained entirely on parenteral fluids for nine days, as shown in Fig. 1. On her second postoperative day, she had several black bowel movements, and by her third day, x-ray revealed air in her rectum. In spite of this, however, not until her ninth day, when a polyethylene catheter was inserted into her stomach, could oral fluids be administered, even by slow drip. Full nipple feedings were tolerated by her twelfth postoperative day, and thereafter her course was uneventful. A gastrointestinal series before discharge showed a normal intestinal pattern. Now 8 months of age, the child is well, has had normal growth and development, is free of digestive disturbances, and weighs 17 pounds.

DISCUSSION

In this infant, intestinal obstruction resulted from a defect in mesenteric fixation associated with an ileal duplication, which permitted rotation around the high and rudimentary attachment of the mesentary, the duplication acting as a leading point for a clockwise volvulus which rotated through four complete turns. Resection of the lesion and repair of the mesenteric defect were performed to prevent further obstruction.

In such an infant with small bowel obstruction for thirty-six hours before parenteral therapy and almost sixty hours before surgery, whose general condition at time of exploration was only fair, the ideal form of bowel surgery remains controversial. Because of high mortality in infants and children, a short-circuiting procedure or exteriorizing operation has been commonly employed. Gross and Ware[3] strongly recommend the aseptic Mikulicz resection in such situations, feeling that this method will give a higher recovery rate to the surgeon dealing only occasionally with intestinal problems. They feel that resection and primary anastomosis are too productive of shock in a seriously ill child because of the time required to complete the procedure, and that an open anastomosis with possible spillage of bowel contents into the devitalized peritoneum is opposed to sound surgical principles. The disadvantage of a double-barreled enterostomy, excess fluid and electrolyte loss, they do not count a serious one, inasmuch as it is easily controlled until repair in six or seven days. Dennis,[4] on the other hand, feels that advantages of rapid restoration of gastrointestinal function, omission of a second operation, and shortened hospital stay argue strongly in favor of primary anastomosis.

If the child with intestinal duplication is in good physical condition, Ladd and Gross[5] resect the bowel adjacent to the lesion and re-establish intestinal continuity by side-to-side anastomosis, for, if large enough stoma is formed, this anastomosis becomes functional sooner than the end-to-end type. Dennis,[6] however, uses an oblique, aseptic, end-to-end anastomosis because it avoids formation of blind pouches and because it necessitates only one suture line, rather than three in the former procedure. He has recently published a series of eight consecutive primary resections and anastomoses in children with in-

testinal obstruction, all of whom survived, six of the procedures being end-to-end anastomoses.[4] Morris, Kirklin, and Waugh[7] of the Mayo Clinic also strongly recommend the use of primary end-to-end intestinal anastomoses in infants and children, citing case histories of two who did well following this procedure. Morentz and Morton[8] recently reported a successful intestinal resection and end-to-end anastomosis in a 2-day-old infant weighing 6 pounds 13 ounces. Our patient further demonstrates the success with which an end-to-end anastomosis may be employed in a small infant. A disadvantage of the procedure, the time required for the anastomosis to function normally after patency is demonstrable, is also evident.

SUMMARY

1. An infant with intestinal obstruction associated with volvulus and duplication of the ileum treated by surgical resection and primary end-to-end anastomosis is described. She is one of the smallest patients to survive such a procedure.

2. The advantages and disadvantages of various types of bowel surgery in infants with intestinal obstruction are discussed.

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INTERNAL PROLAPSE OF SIGMOID COLON IN INFANTS AND CHILDREN

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PROLAPSE of the sigmoid colon in infants and children presents a definite clinical picture, but in spite of this the diagnosis is rarely made. Several standard textbooks refer briefly to this condition.[1, 2, 3] Shapiro[4] studied proctological disorders in children in 2,700 cases and found seventy-four cases of internal prolapse of the sigmoid colon. Most of these seventy-four cases revealed redundancy of the sigmoid which produced symptoms, although he does not describe the clinical picture.

There are two types of sigmoidal prolapse: the external, which descends to the outside through the anus, and the internal, which does not present itself to the outside. This paper deals with the latter, internal or hidden prolapse. We have collected eight cases, two of which are herewith presented.

CASE REPORTS

CASE 1.—M. B., a white female infant, was first seen at the age of 6 weeks. Since 2 weeks of age she had been having six to ten yellow liquid to pasty stools each day. Several of the movements every day were accompanied by considerable straining, pain, and crying. The mother stated that the child sometimes strained so hard that her face became very flushed and that the straining and crying seemed to increase when she picked up the child to comfort her.

The infant was the first offspring of normal parents and had an uneventful delivery. The parents had noticed some straining at stool at 2 weeks of age, and at this time an anal ring was discovered by a physician. This was successfully dilated daily by the mother, but the distress with bowel movements continued to increase.

Physical examination revealed a normal active infant. Rectal and sigmoidoscopic examination revealed an internal prolapse of the sigmoid colon. Barium enema revealed a redundant sigmoid colon. Treatment by maintaining a soft stool and placing the infant in a prone position during defecation was successful in the next two months. At age 6 months a three-day period of constipation occurred with recurrence of original symptoms. The patient is now 9 months of age and has not had any further difficulty.

CASE 2.—M. S., a white male infant, was first seen at the age of 19 months with the chief complaint of passing frank blood-streaked stools, pus, and mucus for three months. The mother stated that the child had hard stools for his entire life and had difficulty expelling feces for the same length of time. The patient had had pain on defecation and tenesmus since the age of 5 months. The pain was of a colicky-like nature.

Physical examination revealed a healthy, active 19-month-old infant. Rectal examination revealed good sphincter tone and no anorectal abnormalities. The prolapsed sigmoid could be palpated with the examining finger when the infant strained. Anoscopic examination was negative. Sigmoidoscopic examination up to 20 cm. revealed a marked redundancy of the sigmoid which was seen to prolapse into the rectum when the child strained. The mucous membrane was thickened,

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edematous, and ulcerated in many areas. Numerous petechiae were seen. The mucous membrane of the rectum was normal. A double contrast barium enema failed to reveal any pathology except for the marked redundancy of the entire sigmoid colon.

The patient was treated with a diet attempting to produce soft stools, regular times at stool, and assurance to the parents. The patient was last seen at 2½ years of age and had not had any difficulty since.

The early signs and symptoms are usually vague in the average case. Constipation is the rule although frequency of bowel movements may precede or bring about the condition. There is marked irritability both before and during a bowel movement. Colicky-like pains accompany the act of defecation; these may be mild to severe. In more severe cases there may be a mild shocklike picture. At

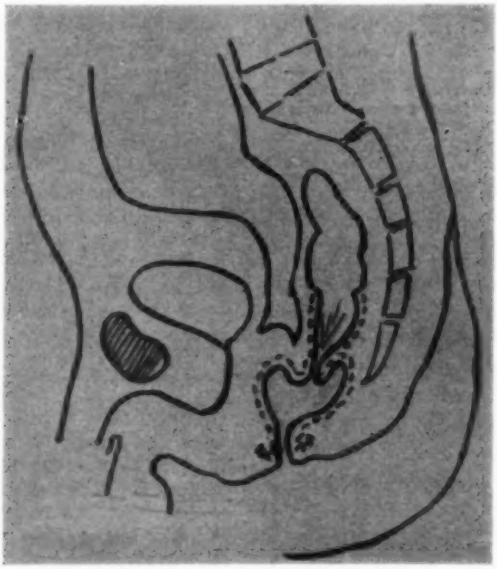

Fig. 1.—The line drawing depicts the internal prolapse of the mucous membrane of the sigmoid colon. As time goes on, the entire wall prolapses, and the condition converts into a chronic, recurrent, nonsurgical intussusception.

DISCUSSION

Some of the etiological factors of internal sigmoidal prolapse are constipation, anorectal abnormalities[5] of any sort causing partial obstruction, lack of the sacral curve,[6] phimosis, etc. Actually, *any* condition that causes undue straining may bring about such a prolapse or aggravate one already present, especially if there is any degree of sigmoidal redundancy.

times in late cases the mucous membrane may become so irritated that there is actual ulceration with the passage of blood, pus, and mucus. This is usually accompanied by an increased frequency of bowel movements. As the condition becomes chronic, due to greater descent of the sigmoid colon, the parent may notice an increased time for defecation to be completed.

The diagnosis may be suspected from the history. In the first stage, increas-

ing irritability is the only complaint. This may be associated with frequent pasty or pasty-liquid stools. As the condition progresses, there is pain and undue straining at the time of defecation. The passage of blood, pus, or mucus with an increased number of movements indicates erosion and ulceration of the mucosa of the bowel and usually occurs in long-standing cases.

The diagnosis therefore cannot be made without *at least a digital examination of the rectum.* It is probable that a great many cases are not diagnosed because a *complete* examination (i.e., a digital and endoscopic examination) is not done. A barium enema is indicated to rule out other possible pathology. This usually reveals a redundancy of the sigmoid colon. The mechanics of administering a barium enema frequently reduces the prolapse.

The prognosis is almost invariably good. The child tends to "outgrow" the condition, as is true of other types of lower bowel prolapse in children. This condition actually represents a chronic, recurrent, nonsurgical intussusception of the lower bowel.

The treatment is of a conservative nature. Assurance of the parents is of utmost importance. Any existing obstructing lesion or abnormality or any factors conducive to straining (constipation, diarrhea, phimosis, etc.) which may have initiated the process should be corrected. The dietary aims should be directed toward a low residue and a soft stool. For older children, an attempt should be made to have their evacuation at the same time every day. Prolonged sitting on the toilet should be avoided. Usually a recumbent position is best, or at times a prone position may be equally or more helpful, especially in infants. Mothers should be cautioned not to hold the child in an upright position when the child is crying and in pain. This position tends to aggravate the condition by sheer mechanics of gravity. Surgical intervention is rarely if ever attempted, in fact, is usually contraindicated in the average case.

SUMMARY

1. The clinical picture of internal prolapse of the sigmoid colon is presented.

2. Two case reports are given.

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PRIMARY TUBERCULOUS INOCULATION OF AN EAR LOBE

Report of an Unusual Case and Review of the Literature

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THIS case is being reported because of the unique circumstances involving a primary inoculation infection with the tubercle bacillus and the satisfactory response obtained with streptomycin therapy.

CASE REPORT

J. G., an 18-month-old white female infant, was admitted to Morrisania City Hospital on Nov. 17, 1950, with the chief complaint of pain and swelling of the right side of the neck of five days' duration. The birth history was normal and the neonatal period uneventful. The child was born in the United States of Porto Rican parents. Two months before admission, the mother had pierced the child's ears for earrings. A piece of string on an ordinary needle was carried through each ear lobe and left in place for about one week. Earrings were then placed into the ears. A month later the mother was hospitalized for active pulmonary tuberculosis. Five days before the child was admitted to the hospital, the father noticed swelling and redness over the right side of the child's neck and the child complained of pain over the same region. The earrings were removed but the swelling and redness persisted, spreading upward behind the right ear. The child became anorexic and feverish.

Physical examination revealed a well-developed, well-nourished, pale child, not acutely ill, with rectal temperature of 100.4° F. There were swelling and induration over the right cervical region extending from below the angle of the mandible and involving the infra-auricular, preauricular, and postauricular groups of lymph glands. The nodes appeared firm and matted together. Both ear lobes showed evidence of having been pierced recently. The right ear lobe appeared swollen, with an ulcerated, crusted lesion in its center and a surrounding area of inflammation. The left ear lobe was normal except for the healed pin-point puncture mark in its center. The remainder of the physical examination was normal.

Laboratory examination revealed the presence of a mild hypochromic anemia (hemoglobin 8.5 grams); other tests were noninformative. X-ray of the chest revealed no evidence of pulmonary pathology. Examination of the gastric contents failed to disclose acid-fast organisms.

The diagnosis on admission was right cervical lymphadenitis. Wet dressings were applied to the affected area and the child received penicillin. Within two days the temperature returned to normal; pain was no longer present, and the cervical mass appeared to have central softening. Three days later, however, the temperature spiked to 104° F. Since the cervical mass appeared semifluctuant, aspiration with a needle was done under aseptic technique, and 3 c.c. of purulent material were removed. This showed acid-fast bacilli on both direct smear and culture. The Mantoux test (1:10,000) done on admission was strongly positive after twenty-four hours.

Streptomycin therapy was begun on an interrupted schedule and 0.5 Gm. was administered daily for three

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weeks, every other day for two weeks, and every third day for three weeks. Para-aminosalicylic acid (PAS), 3 Gm., was given daily during this time and continued for sixteen weeks. During the course of treatment, two doses of streptomycin (50 mg.) were injected directly into the cervical nodes after aspiration. Smears and cultures of subsequent aspirations failed to demonstrate acid-fast bacilli.

The child became afebrile after the second day of streptomycin therapy. She appeared active, alert, and had a good appetite. There was no apparent impairment of auditory or vestibular function. The inflamed ulcerated area in the center of the right ear lobe gradually healed and the auricular and upper cervical nodes decreased in size. After four weeks of treatment with streptomycin the contour of the neck resumed its normal shape.

Fig. 1.—Photograph of J. G. taken Nov. 22, 1950, showing postauricular swelling.

DISCUSSION

It is very likely that the child had tubercle bacilli inoculated directly into the ear lobe at the time the mother pierced the ears with a needle. The mother did not remember whether she moistened the thread with her lips but admitted that she might have done so. Even if tubercle bacilli had not been inoculated into the ear at that particular time, the traumatized area could have acted as a focus for later implantation of the organisms by the mother through close contact with the child.

While no case of primary tuberculous inoculation of the ear lobe was found reported in the literature, Lederer[1] calls attention to the possibility that tuberculosis of the external ear may follow direct cutaneous inoculation. However, he states that this cutaneous inoculation results from transfer of tubercle-laden secretions from middle ear suppuration or as a direct extension from neighboring fistulous tracts. Actually this is secondary inoculation. Other forms of cutaneous tuberculosis affecting the external ear include lupus vulgaris in which the typical "apple jelly" tubercle may be demonstrated. Tuberculosis of the subcutaneous auricular structures may follow direct cutaneous inoculation causing extensive nodular formation and tissue destruction of the underlying cartilage. Hearing is generally not impaired unless the process is secondary to tuberculous otitis media. Lymphadenopathy involving the preauricular, postauricular, and infra-auricular

groups as well as the deeper cervical chains is usually present, as in the case under discussion.

Reports of unusual sites of primary tuberculous inoculation appear from time to time in the literature.[2] These indicate that no organ or tissue is immune to direct tuberculous infection. Among the sites of entry mentioned are the forehead, tongue,[3] cheek, mastoid, eye, salivary glands, tonsils, oral mucosa, lip, middle ear, upper and lower extremities, as well as the genitalia. Because of the unique modes of infection, one may encounter difficulties in diagnosis. For example, Jonsson[4] reports a case of primary inoculation tuberculosis of the right forearm following a cat bite. The child died of tuberculous meningitis three months later. In recent years two cases of tuberculous abscess following intramuscular penicillin injection have been reported.[5] Bass[6] cites the case of an Army officer who suffered superficial wounds of the face lateral to the right eye from shell fragments and wood splinters from a barn door. After removal of the fragments with apparent healing, ulceration developed at the site of injury together with regional cervical lymphadenopathy. A malignancy was suggested, but histological examination of the excised ulcer and lymph node revealed acid-fast bacilli. It has been estimated that primary cutaneous infection with the tubercle bacillus comprises only 0.14 per cent of all primary tuberculous infections.[7]

In essence, the experience cited is a clinical corollary of the Koch phenomenon as observed in the noninfected guinea pig. A healthy guinea pig inoculated with tubercle bacilli develops a small wound which closes and apparently heals, only to become indurated and break down in ten days to two weeks. The regional lymph nodes then become swollen and indurated. Later they undergo caseation necrosis and sinuses may form if healing does not keep pace with tissue destruction. Tubercle bacilli may be isolated from both lesions during the phase of ulceration and caseation. Later the organisms are isolated with difficulty, but may be demonstrable even in the healed scars following excision of the primary focus. The Ghon tubercle in the lung thus has its analog in the primary cutaneous complex.

Treatments formerly advocated for the cutaneous and lymphatic involvement included high vitamin diet, rest, avoidance of sunlight, removal of foci of infection, x-ray therapy,[8] heliotherapy, ultraviolet therapy, carbon dioxide snow, fulguration, incision and drainage, excision, plastic reconstruction, tuberculin injections, and calciferol.[9] At present streptomycin and PAS appear to be the most promising. In the case described the streptomycin regimen followed that used for the adult tuberculous patients except for the proportionally smaller dosage.[10]

Tuberculous lymphadenitis is listed as one of the indications for antimicrobial treatment by the Committee on Drug Therapy in a recent publication.[11] Both streptomycin and dihydrostreptomycin are recommended since neither was found superior to the other and resistant strains of tubercle bacilli were found resistant to both. Allergic reactions (drug fever, dermatitis) are encountered more often with streptomycin. The interrupted regime is recommended unless miliary or meningeal tuberculosis is present. One gram of streptomycin administered intramuscularly every second or third day to adult patients is as effective as the daily administration and the incidence of emergence of drug-resistant strains is reduced considerably. Treatment for six to twelve weeks following clinical recovery is advised. Para-aminosalicylic acid (PAS) is less effective than streptomycin as an antimicrobial agent but appears to delay the appearance of streptomycin-resistant strains when given in combination with streptomycin. Twelve grams daily (adult

dosage) in three to four doses is recommended for a period up to six months.

SUMMARY

1. A case of primary tuberculous inoculation of an ear lobe following puncture for earrings in an 18-month-old Porto Rican child is presented.

2. An ulcerative tuberculous lesion of the right ear lobe with regional lymphadenopathy developed and was successfully treated with streptomycin and para-aminosalicylic acid.

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GENERALIZED CONGENITAL PHLEBECTASIA

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DIFFUSE genuine phlebectasia is rare; most of the cases have been reported in foreign journals. In 1936 Freund[4] described an example and reviewed fourteen others which had been reported previously; Bockenheimer[2] deserves credit for the first adequate description which he made in 1907. Since 1936, seven additional examples have been reported, three in foreign literature[1, 3, 5] and four in American literature.[6, 8] In all of these, the venous dilatation has been of a bizarre channel-type involving particular portions of the body, usually an extremity; in some of these there has been an associated disturbance in growth of the involved part.

Recently I had the opportunity to observe a newborn infant with prominent and fairly symmetrical phlebectasia involving most of the body surface. A review of the literature revealed that no similar example with such generalized manifestations had been reported. Dr. Rudolph Matas[7] with his many years' experience in vascular diseases can recall having seen one similar instance some forty years ago. The example herein reported is the only one in the records of Charity Hospital at New Orleans. Because of the rarity and follow-up observations of this congenital venous anomaly, the case is reported.

CASE REPORT

E. A. F., a Negro female, was delivered spontaneously at term on July 21, 1945, after an uneventful pregnancy. There had been five other pregnancies, each resulting in the birth of a normal infant. The maternal serologic test for syphilis was negative. There was no history of any known vascular disorder in the patient's antecedents.

Examination of the baby immediately after birth revealed the weight to be 3.4 kilograms with all body measurements normal. All vital signs, including blood pressure, were considered normal. Repeated and complete physical examinations showed no abnormalities other than the vascular patterns in the skin; in particular, the fundi were clear, and no lesions were apparent on any mucous membranes.

The outstanding feature was the presence of many bluish, superficially dilated blood vessels. These primarily involved the veins, but there were numerous interspersed prominent capillaries which gave rise to many mottled pinkish areas between the veins. No pulsations or bruits of any vessels were noted; certainly, there were no demonstrable arteriovenous connections. Light pressure applied to the skin surface caused blanching of the capillary beds, but the blue color of the veins remained until stronger pressure was applied. The palms of the hands and soles of the feet were not involved; the face to only a slight degree. Otherwise, the phlebectasis involved the scalp, back, chest, abdomen, and was very prominent over all extremities. The course of the great saphenous (Fig. 1), basilic, cephalic, and superficial epigastric veins and their numerous tributaries could be easily observed. Roentgenograms of the chest and bones revealed no abnormalities.

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This child has been followed periodically in the outpatient clinic. She is now over 6 years old. Her physical and mental development have been normal. There has been a gradual decrease in prominence of the phlebectasia until at present only the veins of the extremities and lower abdomen remain conspicuously enlarged. Her dark racial skin pigmentation has all but obscured the color of the previously described capillary networks. The vital signs remain nomal, and x-rays of the chest show no enlargement of the heart. Roentgenograms of long bones show no growth disturbance. The electrocardiogram is interpreted as normal. The venous pressure in the large right basilic vein is 60 mm. water. There has been no elevation of skin temperature when compared to controls. The sweat glands function normally. Routine blood counts and urinalyses, sedimentation rate, capillary fragility, bleeding and coagulation time are normal. Serologic tests for syphilis are negative. Adequate deep vein circulation has been demonstrated by the comparative tourniquet test.

This child has sustained a number of minor injuries to the lower extremities, but none has been extensive enough to sever any larger veins. Hemorrhage from such an injury might have been a severe complication in phlebectasia of this magnitude.

Since the patient was born, the mother has given birth to two other siblings; both were normal and neither had venous abnormalities.

Fig. 1.—Reproduced from Kodachrome made on the second day of life. Note the numerous dilated veins of the lower extremities.

SUMMARY

A recently observed example of generalized congenital phlebectasia has been reviewed. To my knowledge, no similar instance with such generalized superficial dilatation of the venous system has been reported. As with many vascular nevi, the future course will undoubtedly continue to be benign.

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Symposium on Cerebral Palsy
Part II

SOME EFFECTS OF IONIZING RADIATION AND METABOLIC INHIBITION ON THE DEVELOPING MAMMALIAN NERVOUS SYSTEM

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WITH THE TECHNICAL ASSISTANCE OF CAROLINE A. SCHAUFUS, ALICE A. WILLIAMS, AND REGINA C. COONEY

ABNORMALITIES of the nervous system that are present from birth have many causes. Emphasis has been laid on birth injuries and on genetic faults as causes, but less attention has been given to factors that might interrupt the development of the nervous system during fetal growth. The role of anoxia in producing brain damage at birth is poorly understood and sometimes overrated. This is partly because of the difficulty in distinguishing between asphyxia and the more complex process of arrest of the fetal placental circulation, and the relation of both of these to the metabolic age of the fetus. The variety of malformations that are seen suggests that many may have been prenatal in development. German measles, therapeutic pelvic irradiation during pregnancy, and other agents have been implicated in some such cases but the mechanisms by which they may affect the developing brain are incompletely known.

Experiments with animals were therefore undertaken (1) to determine what are the acute effects of ionizing radiations on the developing embryonic nervous system and what late malformations may develop depending on the time of injury; and (2) to compare these results with the effects produced by various forms of enzyme inhibition. The experiments have revealed that the developing nervous tissue (neuroblasts) are unusually easily destroyed by radiation[1] and that similar reactions can be brought about by certain enzyme inhibitors, some of whose actions may be similar to the chemical actions set up by radiation. Such an attempt to characterize the developing nervous system metabolically in vivo might yield useful information concerning its vulnerability to various injurious agents and the mechanisms by which malformations are brought about. It is the purpose of this presentation to outline the results obtained thus far and to draw some preliminary inferences about fetal brain metabolism that may lead to a better understanding of human cerebral palsy.

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MATERIALS AND METHODS

Essentially the experiments consisted of administering to pregnant animals *acute* sublethal doses of whole

body ionizing radiations, acute sublethal doses of chemical enzyme inhibitors, antimetabolites, anticancer agents, insulin, and acute asphyxia in nitrogen; and then studying pathologically all fetal and maternal tissues at appropriate intervals afterward. The basic methods have been detailed previously.[1, 2, 3] *Chronic* experiments have not been carried out.

Most of the irradiation experiments (several hundred in all) were carried out on rats and mice of pure and hybrid strains, but the susceptibility of chick, duck, turkey, hamster, and guinea pig embryo neuroblasts to destruction by x-rays was checked in a small series. General Electric Maximar therapy units at 200 kv., inherent filter of 3 mm. aluminum, and 10 Ma. with several fixed target distances from 25 to 50 cm. provided the x-rays. The intensity of radiation in air being delivered was checked by a Victoreen apparatus either by placing it with the animals during irradiation or duplicating the setup used for exposing them. A few pregnant animals were irradiated in the Harvard University cyclotron or by being given radioactive phosphorus parenterally. The three forms of radiation acted similarly on neuroblasts. Irradiated animals were studied pathologically at intervals of fifteen minutes to a year after exposure.

The experiments with metabolic inhibition employed a method previously developed[2, 3] that was designed to study the mechanisms by which selective lesions of different parts of the brain and other organs in adult animals are brought about. In principle, a form of acute metabolic inhibition was administered to the pregnant animal in dosage or amount just short of killing it (approximately the acute LD_{50}), on the premise that different tissues have different metabolic patterns and that the tissue or cells most vulnerable to the inhibition would be selectively destroyed.

A battery of agents have been or are being used: acute asphyxia in nitrogen, insulin (hypoglycemia), sodium cyanide, sodium azide, malononitrile, sodium fluoroacetate, sodium 2,4-dinitrophenol, plasmocid (8-[3 diethylaminopropylamino]-6-methoxy quinoline dihydrochloride), sodium p-chlormercuribenzoate, phenylmercuric nitrate, sodium p-iodosobenzoate, sodium fluoride, sodium monoiodoacetate, Mapharsen (m-amino-p-hydroxyphenylarsineoxide hydrochloride), Aminopterin (4-aminopteroyl glutamic acid sodium), nitrogen mustard (methyl-bis [beta-chloroethyl] amine hydrochloride), "TEM" (triethylene melamine), and combinations of sulfhydryl reagents. Other antimetabolites and metabolic inhibitors and combinations of them (sequential enzymatic blocking) are under study. The drugs were given in aqueous solutions or suspensions usually intraperitoneally, to rats and mice in their second and third trimesters of pregnancy, but subcutaneous, intramuscular, and intravenous injections were also employed in some cases. The route employed did not appreciably affect the results in the present acute experiments. Newborn animals were also given the drugs in order to determine by difference what effects might be attributable to the placental barrier. Insulin in single doses (2 to 8 units) was given to both fasting and nonfasting pregnant adult and newborn animals,[2] coma allowed to develop,

and revival obtained with glucose. Asphyxia was administered by immersing the pregnant animal repeatedly in nitrogen to the point of coma, then immediately resuscitating it in air. It was done about every minute and a half for twenty minutes to one hour. This "acute" anoxia procedure fairly consistently produces necrosis of cortical or striatal neurons in adult animals and sometimes is effective after one to three immersions. The repetition is probably not essentially a cumulative effect, but simply increases the likelihood of obtaining one bout very close to lethality. Single doses of insulin to adult rats and mice, briefly fasted and occasionally nonfasting, almost always produces necrosis of cerebral neurons.

Enzyme inhibitors were made up in aqueous solutions or suspensions in concentrations of 1, 5, or 10 mg. per 100 c.c. as suited convenience for injection. Suspensions and sodium salts of iodosobenzoic and chlormercuribenzoic acids were both used with no apparent difference in effect. The doses most often used were single although azide, malononitrile, and cyanide were sometimes given in two to four divided doses within an hour to attain more easily a near lethal effect.[2, 3] Mustard, TEM, the mercury, iodine, and arsenic compounds, fluoride, and Aminopterin were given in single doses, for their effects were either adequate that way or of sufficient duration not to warrant repetition. The doses used, then, usually approached the acute LD_{50}, and killed occasional animals in each experiment. Most frequently used were, in milligrams per kilogram of animal weight: cyanide, 4 mg.; malononitrile, 10 mg.; azide, 5 to 10 mg.; dinitrophenol, 10 to 15 mg.; plasmocid, 16 mg.[3]; fluoroacetate, 2 to 3 mg.; Mapharsen, 20 mg.; chlormercuribenzoate, 50 mg.; iodosobenzoate, 150 mg.; phenylmercuric nitrate, 75 to 100 mg.; iodoacetate, 30 mg.; fluoride, 50 mg. Aminopterin, TEM, and mustard were usually used in doses that did not come close to the rapidly lethal dose, but which often did cause death of the adult days later due to bone marrow damage. Severe acute fetal damage could be obtained when less than a milligram of TEM, mustard, or Aminopterin was given to a 25 to 30 gram pregnant mouse. Newborn animals were given proportionate adult doses.

The pathologic procedures have been described in part before.[1, 2, 3] For acute experiments where acute necrosis of neuroblasts or other tissues was the end result being sought, animals were usually killed sixteen to twenty-four hours after metabolic injury by severing the thoracic spine, and samples of all organs and tissues including several muscles were made of the adult, and interrupted serial or less frequent sections were made of the adult brain and the fetuses. Several placentas were examined in each litter. Fixation was usually in Bouin's picric-acetic-acid formalin, embedding in paraffin, and sections stained with hematoxylin and eosin, but a number of other methods of preparation and staining (viz.: freeze-dry, histochemical) have been used. The end point, or criterion of effect, in these acute experiments was destructive lesions—necrosis—of various cells, cell groups, or tissues, as outlined previously.[1, 2, 3] In experiments where the fetuses were permitted to survive for several days or to be born and grow to adulthood, the end point

or criterion of effect was malformation or defective development of the nervous system and other tissues.

RESULTS

General.—The aim of these experiments was to determine whether certain agents damage the developing nervous system and other tissues, by what biochemical means they may do it, and by what biochemical and anatomic mechanisms they may produce developmental malformations. The results may best be presented first in a few general statements, then followed by pertinent details, and discussed below.

In respect to the effects of *ionizing radiations,* the developing rat and mouse nervous system in the second and third trimesters was found to be the most sensitive of all tissues to destruction by ionizing radiations.[1] X-rays, when given in doses as low as 40 r to the whole body of pregnant mice, selectively destroyed developing cells of the nervous system, "neuroblasts," in the young (Fig. 1*a*). Surviving cells proliferated rapidly, forming abnormal patterns, so that in fetuses that lived and grew up a variety of deformities of the nervous system resulted (Figs. 2, 3, 4, 5, 6). Neuroblasts in newborn animals during their first week were equally susceptible. The character of the malformation depended critically upon the time that the x-rays were given during pregnancy or after birth, and these are summarized in Fig. 7. These critical periods have been found to be fairly rigid. Some of the nervous system malformations were accompanied by skeletal and visceral deformities. The critical periods for these grossly evident anomalies have been worked out in great detail by Liane B. Russell at Oak Ridge and many of them confirmed in this laboratory, especially when they related to abnormalities of the nervous system. Ionizing radiation causes abnormal brains to develop by actually destroying certain building blocks. In the case of other tissues it acts less vigorously by slowing the building process for destructive lesions have not been seen in the lower dose ranges.

With regard to the experiments dealing with *metabolic inhibition,* three sulfhydryl reagents (Mapharsen, chlormercuribenzoate, iodosobenzoate), an antimetabolite (Aminopterin), and two anticancer agents (nitrogen mustard, TEM) produced destruction of neuroblasts in a pattern not qualitatively distinguishable from that produced by radiation. Combinations of some of these drugs did the same. Plasmocid and fluoroacetate also imitated the radiation pattern. In contrast, insulin hypoglycemia damaged (though rarely) more mature cells and spared the neuroblasts, thus resembling the adult pattern of injury from hypoglycemia.[2] Cyanide also produced an unusual pattern: in several litters of both rats and mice near term it singled out for destruction young neurons in the dorsal part of the cervical cord, spared all other regions except some young cortical neurons and "white" matter frontal to the striatum. Acute asphyxia, malononitrile, azide, and dinitrophenol caused no fetal lesions. Iodoacetate and fluoride also failed to damage the fetal nervous system when given alone.

Nitrogen mustard and especially TEM when given in any but minimal doses damaged other cells than growing neuroblasts in the fetus although

neuroblasts were the most severely affected. TEM damaged fetal cartilage almost as readily as it did neuroblasts; nitrogen mustard did so less. None of the other agents destroyed cartilage and it is interesting that destruction of cartilage did not occur with radiation up to 400 r, although the skeletal malformations that result, even with low dosage,[4] indicate a sublethal dam-

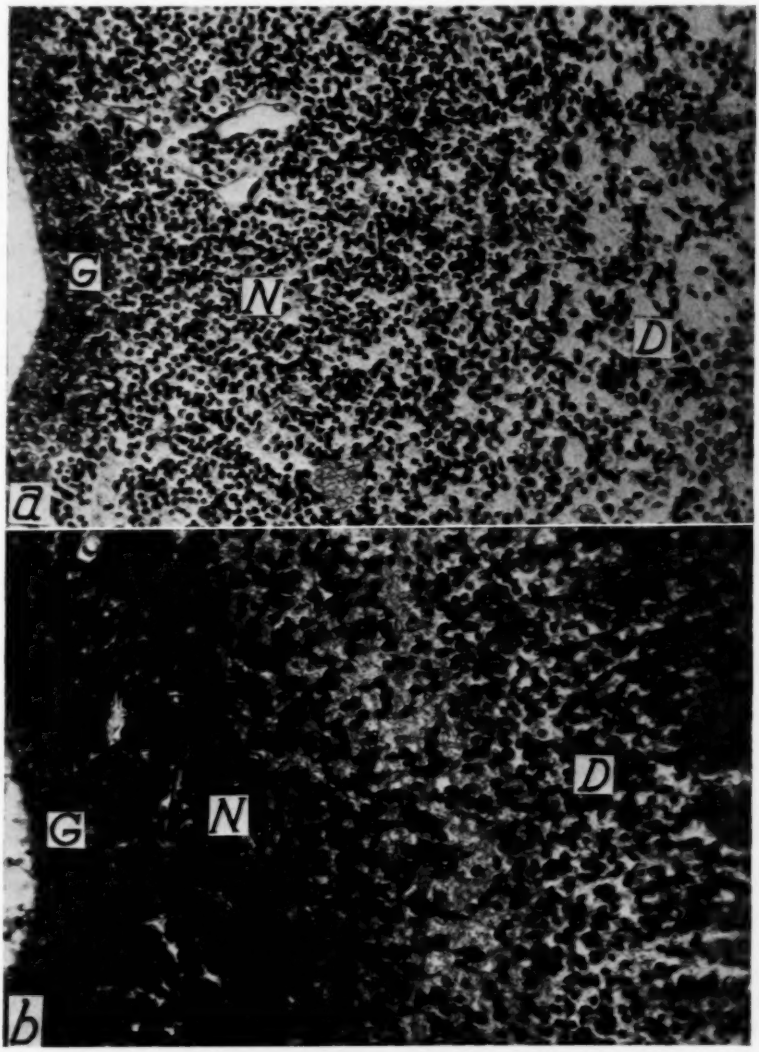


Fig. 1.—*a*, Acute radiation necrosis of neuroblasts. Primitive neurectodermal germinal cells lining the ventricle at *G* are resistant. Developing neuroblasts at *N* (small dark cell remnants) are necrotic. Fairly well differentiated nerve cells at *D* are preserved. *b*, Acute damage of the cortex following hypoglycemia near term. Germinal cells and neuroblasts at *G* and *N* are resistant to hypoglycemia, but more mature nerve cells at *D* are necrotic. (Hematoxylin and eosin, about ×300.)

age to these cells. Late skeletal malformations that might develop following exposure to these chemical agents have not yet been worked out. Chlormercuribenzoate and plasmocid, and to a lesser extent Mapharsen, iodoacetate, and iodosobenzoate, caused necrosis of fetal skeletal muscle fibers. The distribution of these lesions and the possibility of late developmental abnormalities of muscle and "muscular dystrophies" remain to be solved.

low 70 r to check the lower limit of susceptibility. The lower limit for chicks, hamsters, etc., has also not been measured. The destructive effects vary in distribution fairly consistently with the dose and with the age of the fetus. At 40 r necrotic cells appear as a rule only in the anterior striatal periventricular region and at the angle of the lateral ventricles where the corpus callosum is forming. As the dose increases more of the deep basal nuclear

A. *B.*

Fig. 2.—Radiation microcephaly. *A*, Normal adult rat brain. *B*, Brain of adult rat whose mother received 150 r about the sixteenth day of gestation. The forebrain is small, exposing the midbrain. The cerebellum is somewhat grossly malformed but the brain stem and cord are normal in size.

Results of Ionizing Radiation.—X-rays, when given as described from 40 to 600 r,[1] selectively destroyed varying numbers of neuroblasts in the brain, cord, retina, and ganglia of mice. At 40 r some fetuses show few or no necrotic cells, the number increasing to a maximum at 150 to 200 r. The same applies to rats although measurements have not been made be-

masses and cerebral cortical neuroblasts are involved, then the growing dorsal, ventral, and central cells in the spinal cord, and last the retinal neuroblasts. The cortical neuroblasts are nearly as susceptible as those of the striatum. This order of susceptibility is modified by the age of the fetus so that order of susceptibility is an approximation. First, as gestation

proceeds, the cord becomes decreasingly effected as does the retina. Second, the central nervous system is unaffected by up to 300 r during the first eight days of gestation but a sharp change occurs about the ninth day and it becomes very susceptible. This is partly because at this point the "neural tube," which has been composed of primitive neurectoderm, starts to differentiate, and neuroblasts* begin to proliferate and grow from the central tube. It is these developing, growing cells that are consistently radiosensitive (and sensitive to certain enzyme inhibitors) throughout fetal and newborn development, while the central more primitive neuroectoderm is partially or quite resistant. In a way, this situation may be analogous to the resistant primitive germinal reticular cells and the radiosensitive lymphocytes in a lymph node. This contrast is shown in Fig. 1*a*. Radionecrosis is full blown histologically in four hours, either in a fetus or in a newborn animal, and clearly evident in many cells in two hours, indicating that the effect is a direct one. Neuroblasts in mitosis are affected but the majority of the necrotic cells are not dividing. That the mitosis is not a prime factor in this radiosensitivity is shown by the appearance of mitoses in the central germinal neurectoderm within four hours after radiation. Another reason is that at the time the dorsal spinal cord cells are most sensitive they have passed the dividing stage and are simply growing and differentiating.

*Some of these "neuroblasts" are undoubtedly developing glia and ependymal cells but they are so undifferentiated that the broad use of the term neuroblast is presently justified. The term will be used for all stages of these developing cells between neurectoderm and fairly mature, but still growing, young nerve cells.

Within twenty-four to forty-eight hours a peculiar type of proliferation develops from the remaining neurectoderm and neuroblasts. This is the formation of abortive neural canals and rosettes. This may be an inherent growth characteristic or more reasonably it may be that necrotic neuroblasts, rich in nucleoprotein residues, act as organizers and stimulate such "neural tube" and rosette growth.[5] This process progresses, necrotic material is rapidly engulfed by phagocytes, and a variety of malformations result. The character of the malformation is determined largely by the time of radiation, but also by the dose. No neural malformations have resulted from radiation up to 300 r before the eighth day of the approximately 21 days of gestation for the mouse and rat. Embryos so treated have grown up with brains apparently normal in all respects. Studies have not yet been made, however, to determine whether other visceral anomalies have occurred in this period. On the ninth day the most striking externally visible malformation occurs. This consists of encephalocele or partial anencephaly accompanied by malformation of the skull and face (Fig. 3). When born the animals do not live, or they are soon eaten by the mother. The mechanism of this malformation is not simple and the anatomic sequence is presently being studied. Preliminary work suggests that at this period the neural tube of the posterior part of the forebrain is still closing and also that this part is beginning to differentiate and hence becomes radiosensitive. The principal neural deformity that results is a defect of the upper part of the cerebrum with varying degrees of head deformities. Much

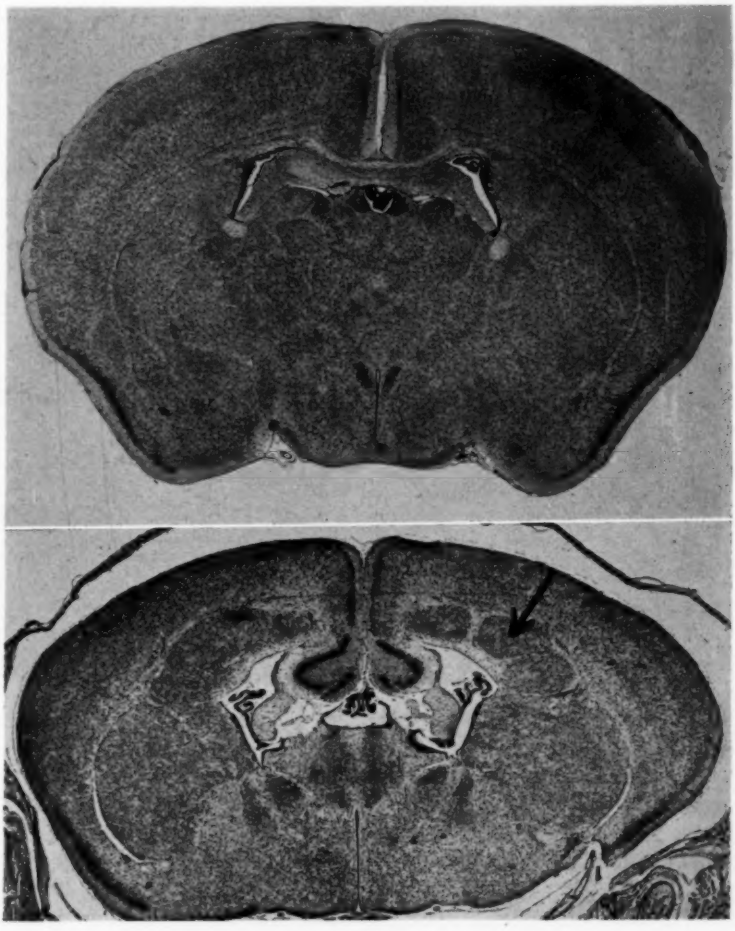
more study is needed before this brief explanation can be accepted. Irradiation on the ninth and tenth days is characterized late by a deficient cerebral cortex, dilated cerebral ventricles ("hydrocephalus"), and a deficient or nearly absent hippocampal formation. Irradiation after the tenth day produces a series of patterns of malformations: bizarre rosettes and malformations of the hippocampal nerve cells, malformed cerebral cortex with a tendency for nerve cells to be clustered or actually form rosettes, distortion of the striatum, and absent corpus callosum (Fig. 4). These patterns overlap and the exact timing when each deformity is maximal is still to be worked out. As gestation draws to a close the cerebellum begins to develop rapidly and irradiation carried out during this period or for several days after birth affects the outer cortical zones of neuroblasts with resulting deficiencies of granular and molecular layers and gross distortions of the folia when the animal attains adulthood (Fig. 5). Granular layer defects seem most conspicuous when injury occurs after birth, while gross folia defects are evident when injury occurs late in gestation (Fig. 2). The cerebral cortex during the period has less radiosensitive cells and the zone of neuroblasts that is still forming the medial striatum, though susceptible to radiation, is small in bulk. Hence very serious cortical and striatal distortions such as can be produced earlier do not occur. As the animal becomes an adult the cerebellum is the last to show developing radiosensitive

Fig. 3.—Radiation malformations in newborn rats. *A*, Three animals of a litter of twelve at term who were irradiated on the ninth day of gestation. Heads and brains are extremely malformed. All twelve showed similar deformities. *B*, A litter of four newborn animals irradiated on the thirteenth day. They have externally unremarkable heads but the feet are malformed.

neuroblasts, but for several months there are small cells with compact nuclei subependymally at the angles of the lateral ventricles that resemble neuroblasts in their radiosensitivity. These cells are also destroyed by certain radiomimetic drugs such as triethylene melanime and nitrogen mustard in young adult animals.

Cataracts have developed in some year-old animals and high doses of radiation affect the development of the lens in its early formative period; data on this are incomplete at present.

A.



B.

Fig. 4.—Late radiation malformation of the brain. *A*, Normal rat brain. *B*, A comparable section in the case of a rat irradiated in the latter third of gestation. The basal ganglia are especially malformed, the cortex narrowed, and the corpus callosum absent. The brain is smaller than indicated by the magnification used. (Hematoxylin and eosin, low powers.)

Retinal malformations may result from radiation throughout the period that neuroblasts are present.

Brief note may be made of the appearance, survival, and behavior of these malformed animals although detailed neurological examinations have not been made. Nine- and some 10-day animals do not survive, as noted. Fetuses irradiated on any of the first eight days of gestation apparently have no nervous system abnormalities and when examined a year later show no remote central nervous system effects. Possible deformities of other organs and the peripheral nervous system have not been studied as yet. Animals irradiated on any day after the tenth, up to 200 r (studies on 300 r animals are incomplete), survive with a variety of deformities as described. Eleven-, 12-, and 13-day animals have an irregular waddling gait and seem moderately clumsy when examined closely, but casual inspection of resting animals does not reveal striking abnormalities. The heads are slightly smaller and shorter than normal, and some but not all animals may be a little dwarfed. The eyes may appear slightly small and the palpebral opening may be almond-shaped and superficially reminiscent of the mongoloid. (See Liane B. Russell[4] for details of such malformations.) These animals eat, bite, and climb, and seem to get along with other similarly abnormal or normal rats. Fig. 6 shows x-rays of year-old rats whose mothers received 150 r on about the twelfth day and the thirteenth day of gestation compared with a normal rat. The 12-day rat has only three toes on the hind feet, the thumbs are poorly formed on the front. It and the 13-day rat have short necks due to shorter than normal vertebrae, and the 13-day animal has malformed lumbar verte-

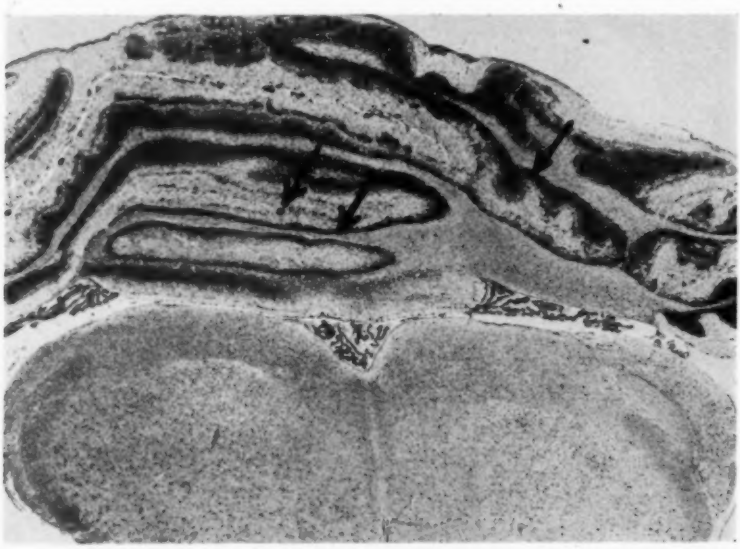
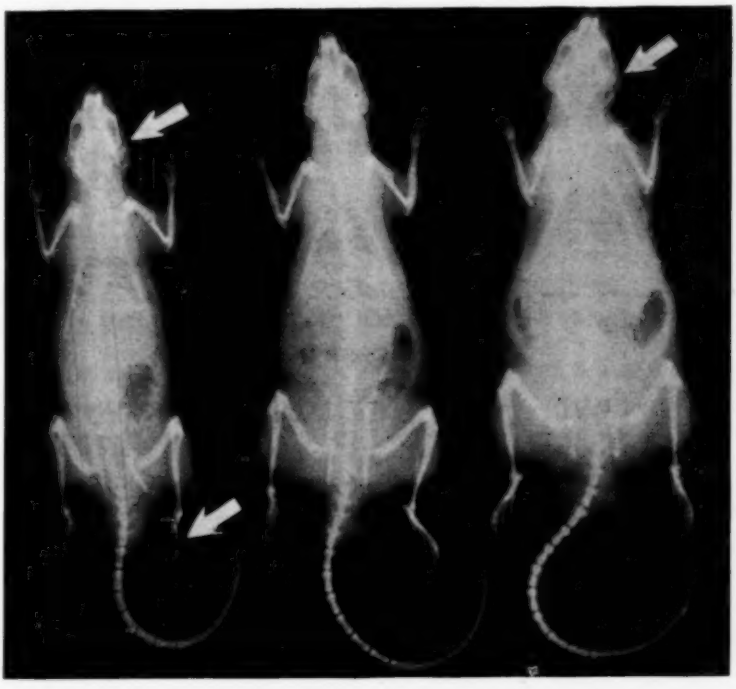


Fig. 5.—Late radiation malformation of the cerebellum. Adult rat that received 190 r total body radiation six days after birth. The granular layers are distorted and clusters of cells out of place in the molecular layers. (Hematoxylin and eosin, low power.)

brae. The skulls are imperfectly formed and slightly smaller and shorter than normal. Irradiation on subsequent days of gestation produces animals that usually appear normal externally but whose brains are malformed. Some of these have reproduced but otherwise no behavior studies have been made in this area. Animals irradiated toward term and especially during the first week of their birth may be clumsy and ataxic and easily pushed over on their sides from the standing position. The cerebellum of one such animal is shown in Fig. 5.



A. *B.* *C.*

Fig. 6.—Late radiation malformations. X-ray picture of three adult rats. *A*, Irradiation about the twelfth day of gestation. *B*, Normal. *C*, Irradiation about the thirteenth day. Irradiated rats have shortened heads and necks, lumbar spinal defects (invisible in photograph), and 12-day animal has only three toes on the hind feet.

Several factors have a bearing on the accuracy of radiation (and other metabolic inhibiting agents) as a tool for studying developmental malformations of the nervous system. Fetal age was estimated by counting from the time of copulation or counting backward from the time of birth. The latter is the less accurate and was used mostly for pilot experiments; the spermatozoa method is used for planned timing experiments. Spermatozoa were observed by examining daily the vaginal contents of breeding females and arbitrarily considering their presence as indicating the first

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day of gestation. Virgin or non-nursing multiparous animals were used to avoid delayed implantation. The large number of animals used, and the remarkably consistent distribution, within limits, of the radiation necrosis tend to make possible a reasonably accurate procedure. However, even individual litter mates have biologic differences and may have had slightly different implantation times so that all of these factors make the procedure one of approximation.

likely other prosthetic groups. Hence in these experiments sulfhydryl reagents, and certain compounds whose pathologic effects resemble those of acute radiation, figure prominently in the list of metabolic inhibitors chosen.[6, 7]

The experiments performed are outlined in the following paragraphs. Litters usually contained five to nine young so that a substantial number of animals was used. Variation in response within the litter occurred, as

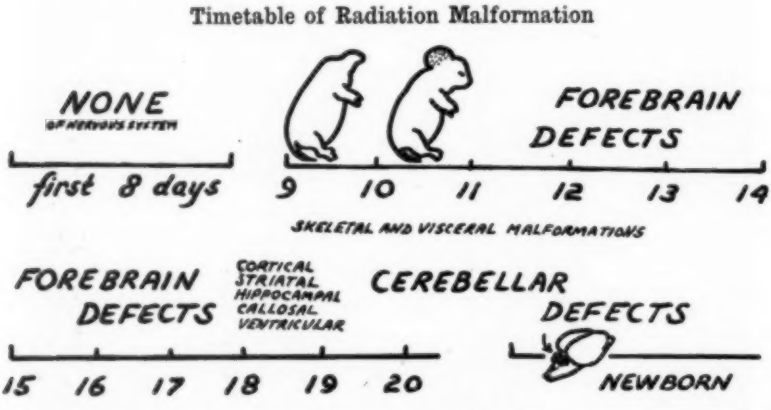

Fig. 7.—Approximate schematic summary of radiation malformations. Preliminary data suggest that radiomimetic drugs may simulate this schema while other agents may produce a different picture.

The duration of pregnancy of mice and rats may differ slightly, but for the present an approximation of 21 days has been a useful figure.

Results of Metabolic Inhibition.—Ionizing radiation probably acts by producing chemical reactions in the cell that are especially active in inhibiting enzymes with free sulfhydryl groups.[6] Radiation may act by ionization of water in the presence of oxygen to produce hydrogen oxides from water, whose oxidation-reduction potential range parallels those of a number of sulfhydryl groups, and very

in groups of adult animals, so that a litter often provided an indication of an LD_{50} when several fetuses were dead. A single such experiment with fetuses showing damage would then have considerable significance. Results do not include animals (either adult or fetal) that died in less than four hours or adults that were found dead.

Acute Asphyxiation in Nitrogen.—Five pregnant mice between 15 and 20 days' gestation were studied for acute injury. Four of five adults showed scattered necrotic neurons in striatum but fetuses were undamaged.

It has not been possible to press these acute episodes of anoxia further, for then the adults die. The result indicates that the fetus is relatively resistant to acute anoxia.

This experimental procedure involves acute anoxia of brief duration which tends to damage adult cells that have no anaerobic energy reserve.[2] It is to be distinguished from placental circulatory arrest[8] which cuts off not only oxygen but diffusion of carbon dioxide and substrates.

Insulin Hypoglycemia (Insulin, Lilly, U 80).—Three pregnant rats, twelve pregnant mice (13 to 21 days' gestation and one litter about 8 to 9 days), and several newborn rats and mice were given 2 to 8 units of insulin subcutaneously or intraperitoneally usually after fasting twelve to sixteen hours.[2] All adults developed deep hypoglycemic coma in three to five hours; this was followed by glucose which revived all but two. Twenty-four hours later adults and fetuses were examined pathologically. All but one adult sustained necrosis of striatal and occasionally cortical neurons. Several fetuses in one litter were dead and all in another litter had died. Death of fetuses had been recent for they were fresh and autolysis was absent. All fetuses but two litters escaped injury: in the one litter (near term), in which some animals were recently dead, there was necrosis of the deeper layers of fairly mature cortical nerve cells of the brains of fetuses, with no damage to the outer zone of still developing neuroblasts or the periventricular neuroblasts of the deep developing basal ganglia. This pattern was in many respects just the opposite of the pattern of injury from radiation or radiomimetic compounds (mustard, Aminopterin, etc.) (Fig. 1*a* and *b*). In addition, fairly mature neurons in the brain stem and in the cerebellum were necrotic while neuroblasts were spared. Similarly the dorsal fairly mature nerve cells of the cervical cord were necrotic (compare with cyanide). In substance the pattern was considerably more like adult hypoglycemic injury[2] than "embryonic" response to radiation. In contrast one litter, whose age was estimated at 8 to 9 days, showed considerable necrosis of many cells throughout the bodies of the embryos but not especially those of the neuraxis. This generalized "patchy" effect needs further study as does the whole problem of embryo metabolism during the first third of gestation.

Since adult brain damage occurred almost regularly in these experiments and the neuroblasts escaped, these cells may be said to be resistant to hypoglycemia. Still more significant is the fact that when the fetus is selectively damaged by lack of glucose the neuroblasts are still resistant (despite their rapid growth), whereas the more mature neurons are susceptible. Death of the fetus, without selective damage, as occurred in another younger litter (between 14 and 17 days) is ascribed to an over-all metabolic effect as occurs with other extreme forms of inhibition.

Newborn mice and rats did not become comatose with insulin but some showed scattered necrotic cortical neurons similar to those seen in adults.[2] Coupling newborn and fetal data, it seems that dependence on glucose in the nervous system increases with maturity of nerve cells, as seems to be the case with oxygen (see Himwich in discussion below).

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Cyanide (sodium cyanide).—Seven pregnant rats, three pregnant mice (14 to 21 days' gestation), and several newborn rats and mice were studied for acute injury. In two litters of mice and two litters of rats consistent patterns of injury developed: necrosis of the fairly mature, though still young, nerve cells in the dorsal cervical spinal cord and in fewer animals some necrosis of similarly developed cells in the anterior cerebral cortex and its underlying white matter. This pattern, like that of hypoglycemia, differed from radiation effect, but in turn it also differed somewhat from hypoglycemia. The lesions developed in animals near term, no embryos below about 14 days were studied. No lesions occurred in the newborn animals tested although some were killed by cyanide. A dose about twice that of the adult[2] was required.

That any cyanide sensitivity should appear in these fetuses when acute anoxia failed to do damage is probably explained by the longer duration of the cyanide action compared with asphyxia. It is known that sustained anoxia may cause fetal damage.

Nitrogen Mustard (methyl-bis[beta-chloroethyl] amine hydrochloride).—Eleven pregnant mice, eight pregnant rats (13 to 21 days' gestation), and several newborn rats and mice were studied for acute injury four to seventy-two hours after the drug. Two additional pregnant rats were treated and allowed to go to term, and the young grew to adult state. All fetuses showed neuroblast necrosis similar to radiation injury. This became evident microscopically in less than four hours like the radiation effect. A few were killed by the process, others had damage to other tissues, still others showed injury limited to the nervous system, depending on the dosage. Similar reactions occurred in the newborn. After forty-eight to seventy-two hours rosettes and bizarre clusters developed in the remaining neuroblasts similar to that following radiation. Heavier doses produced necrosis not only of nervous elements but also of gut epithelium, lymphoid and hemopoietic cells, occasionally testes, paranasal sinus epithelium, and sometimes young cartilage cells. Muscle damage was not seen. The mothers showed, after heavier doses, depletion of lymphoid and hemopoietic cells, and necrosis of epithelium in the bottoms of crypts in the mucosa of the small intestine, just as in radiation. Ovarian follicular granulosa cells were also sometimes damaged. In the brain in young adults small subependymal embryonic cells and some oligodendroglia were necrotized. No other tissues were destroyed.

Radiation injury is so highly specific in its destruction of neuroblasts in the lower dose ranges (below 150 r) that the mother shows no significant ill effects and the lymphoid and blood-forming cells of both adult and fetus are not destroyed. Nitrogen mustard, and, as will be seen, TEM and other drugs also, do not possess this wide margin of difference between effects on adult and fetus. Consequently it has been more difficult to produce malformations without risk to the mother, especially by way of the bone marrow. The two litters that were allowed to grow up sustained mild injury about the seventeenth and nineteenth days of gestation. Malformation took the form of jumbling of the outer lateral and medial cerebral cortical layer with a bunching or clustering of neurons (Fig. 8). The bulk of the striatum ap-

peared reduced compared with the normal. Other abnormalities were not seen, probably because of the timing, for external nitrogen mustard malformations have been reported by Haskin[9] and might be presumed to resemble those of radiation.

"TEM" (triethylene melamine, given in suspension of ground-up tablets obtained from Tumor Therapy Laboratory, Children's Hospital, Boston).—Sixteen pregnant mice (14 to 21 days' gestation) and several newborn mice and rats were treated and studied pathologically twenty-four hours to five days afterward. (An additional nine pregnant mice and one rat died within twenty-four hours of the injection and showed autolysed fetuses; no microscopic studies were made.) All fetuses and newborn mice and rats examined showed a picture similar to that following nitrogen mustard but it was often more severe and spread to other tissues more widely with heavier doses. Fetal cartilage was nearly always damaged.

In the *adult* the lymphoid and blood-forming cells were destroyed with the larger doses, and in three adult animals necrosis of the granular cell layer of the cerebellum occurred and in one of these the uterine mucosal epithelium and islet of Langherhans cells were necrotic. Subependymal cells and oligodendroglia were sometimes necrotic as in nitrogen mustard.

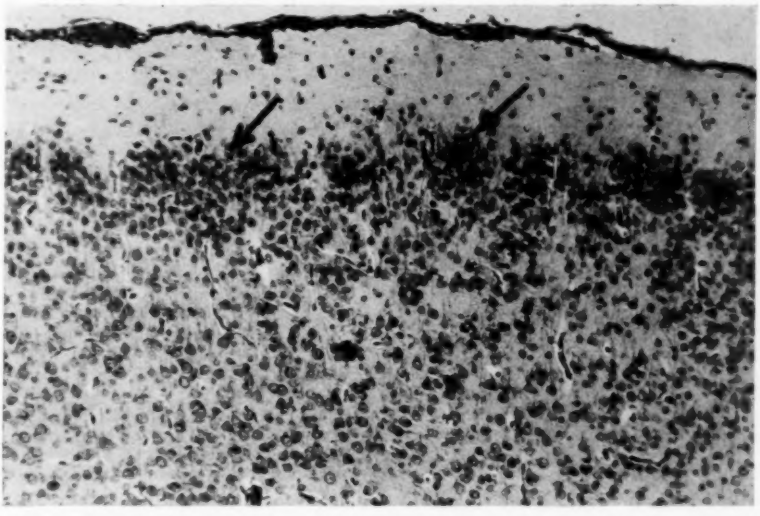

Fig. 8.—Late nitrogen mustard malformation. Distortion of cerebral cortical nerve cell architecture in young mouse whose mother was given a small dose of methyl-bis (beta-chloroethyl) amine hydrochloride about the sixteenth day of gestation. (Hematoxylin and eosin ×300.)

As after nitrogen mustard it was difficult to get damaged fetuses to survive because the bone marrow effects in the mother often led to her death after a few days. In fetuses that survived five days there were retinal rosettes (Fig. 9) and bizarre patterns of growth of neuroblasts in the cortex and striatum similar to those that follow radiation. In some of these fetuses the brain damage was overwhelming

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yet the fetus continued to grow as did its remaining parts of the nervous system.

Long survival experiments have not been completed yet. The predilection of this drug for nervous and skeletal systems suggests it as a useful tool for studying malformations.

Aminopterin (4-aminopteroyl glutamic acid sodium, lot No. 7-7177, March, 1951, Lederle).—Six pregnant mice (15 to 19 days' gestation) and several newborn mice were studied twenty-four hours to five days after treatment. Neuroblastic necrosis resulted in all animals and was indistinguishable from that following radiation and lower doses of nitrogen mustard. As in mustard and TEM the margin between fetal and maternal death is narrower than after radiation and late malformations have not yet been studied. After five days, however, in two litters (Aminopterin in low dose on sixteenth day of gestation) there was irregular growth and some jumbling of the cerebral cortex.

Adult lesions were destruction of lymphoid and blood-forming tissues, gut epithelial necrosis, and in two animals scattered necrotic myocardial cells similar to those described previously after other drugs.[3]

Malononitrile (Malononitrile, Winthrop-Stearns).—Four pregnant mice (15 to 20 days' gestation) studied twenty-four hours after treatment showed no fetal changes. None of the fetuses was dead either, but scattered necrotic striatal neurons developed in two of the adults. There were also more adult ovarian follicular granulosa cells made necrotic than normally. More studies are needed in this group for comparison with cyanide, although using the adult as a base line the indication is that the drug was pressed close to the lethal limits.

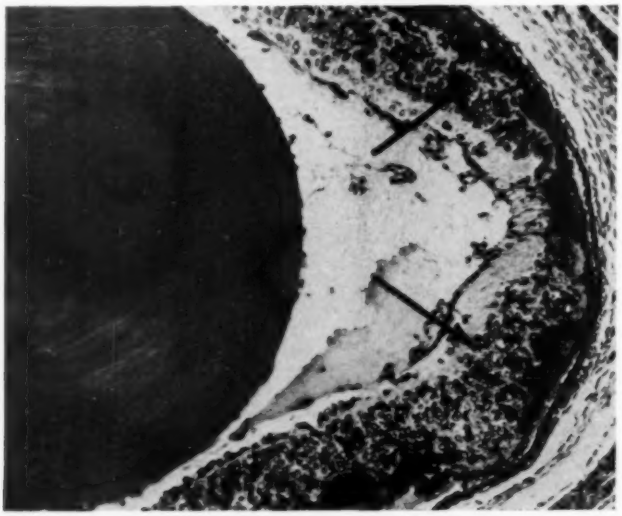

Fig. 9.—Early malformation of the eye following TEM (triethylene melamine). Rosettes and distorted growth of the retina of a newborn mouse whose mother was treated with TEM five days before. The brain was severely damaged. (Hematoxylin and eosin ×300.)

Azide (sodium azide).—Four pregnant rats and two pregnant mice (15 to 20 days' gestation) showed no fetal lesions although some animals were dead in three litters. Fetuses of another rat were allowed to grow to adulthood. Their brains were negative.

Plasmocid (8-[3 diethylaminopropylamino]-6-methoxy quinoline dihydrochloride, from Antimalarial Drug Repository, National Institute of Health, designated "Columbia University Elderfield, Lot TW-25 Plasmocid di HCl").—Two pregnant rats, four pregnant mice, and several newborn rats were studied acutely and after intervals of several months. In the newborn and fetuses neuroblast necrosis occurred and also a considerable number of skeletal muscle cells were necrotic, but heart muscle was spared.

This pattern differed from the adult (previously reported[3]) where skeletal muscle, gasserian ganglion, and heart muscle were attacked. In some young adults, as after certain chemicals (mustard and TEM), small subependymal cells at the angles of the lateral ventricles were also necrotized, but unlike the effects of radiation, TEM, and mustard, plasmocid did not damage oligodendroglia.[10]

Fluoroacetate (sodium monofluoroacetate).—Five pregnant mice and one pregnant rat (16 to 21 days' gestation) and several newborn rats and mice were studied twenty-four hours after injection. In one litter of fetuses necrosis of neuroblasts occurred, and in another slightly irregular neuroblast growth and scant necrosis were seen after twenty-four hours. In the adult, heart lesions as previously reported were present and in one case slight diaphragmatic skeletal muscle damage occurred, a finding not seen in a large number of other animals previously.[3] Fluoroacetate blocks the utilization of two and three carbon fragments aerobically through the citric acid cycle so that these neuroblast findings are of especial interest.

Dinitrophenol (sodium salt of 2,4-dinitrophenol prepared in solution).—Four pregnant rats (15 to 20 days' gestation) were studied after twenty-four hours. Some of the fetuses in two litters were dead, others showed liver hemorrhages, and some placentas were markedly congested. There were no lesions of nervous tissue. Fetal death indicates that the drug was used to the maximum possible.

Phenylmercuric nitrate (aqueous suspension).—Two pregnant mice (about 13 days' gestation) showed no fetal lesions after twenty-four hours, but no fetuses were dead. Mothers showed no lesions, but one of two other (male) mice given same single sublethal doses showed necrosis rarely of skeletal muscle fibers and occasional proximal convoluted tubule cells. These experiments need to be expanded because the dose may not have approached the LD_{50} for fetuses, although it approximated the adult LD_{50}.

Iodosobenzoate (suspension of acid, or sodium salt prepared in solution from p-iodosobenzoic acid, Sigma).—Three pregnant mice (16 to 20 days' gestation) and several newborn mice. (Six others died within twenty-four hours, fetuses recently dead, not examined histologically.) All three litters after twenty-four hours showed neuroblastic necrosis, though in two it was considerably less than after moderate radiation, mustard, etc. In one, cerebral cortical growth was progres-

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sing irregularly; the pattern was somewhat like that after chlormercuribenzoate (Fig. 10). In one litter skeletal muscle cells were occasionally necrotic, and there was patchy necrosis of fetal fat pads. In the mothers and other (male) adults, lesions were absent or there was necrosis of some skeletal muscle fibers in the diaphragm and lateral abdominal wall. Rarely necrosis of crypt cells in the gut, as in radiation, occurred.

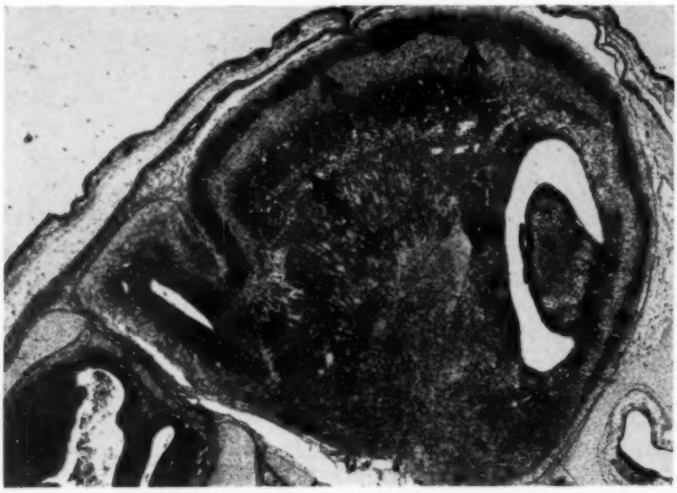

Fig. 10.—Acute chlormercuribenzoate damage to the fetal mouse brain (twenty-four hours). The cerebral cortex shows not only necrosis of neuroblasts, but the remaining cells already show an irregular growth pattern. (Hematoxylin and eosin, low power).

Chlormercuribenzoate (suspension of acid or sodium salt prepared in solution from p-chlormercuribonzoic acid, Sigma).—Six pregnant mice (12 to 20 days' gestation) were studied after twenty-four hours. Four groups of newborn mice were studied from twenty-four hours to three weeks after being treated. Five of the litters of fetuses showed neuroblast necrosis, including the retinas in one. There was also early malformation of the cortex in two litters characterized by irregular growth of the remaining cells (see Fig. 10). The extent of neuroblastic damage was often greater than after iodosobenzoate. Also damaged in many was fetal fat tissue and a fair number of skeletal muscle fibers. Cartilage cells, lymphoid and hemopoietic tissues were not destroyed.

In the newborn animals there was patchy, scattered, not extensive necrosis of the developing neuroblasts of the outer cerebral cortex and sometimes the hippocampus. Striatal neuroblasts were rarely damaged. The picture in both newborn and fetus resembled that resulting from low to moderate doses of radiation.

Adults, including the pregnant ones, sometimes showed one or more of three lesions. In two, one male and one of the pregnant mothers, there was necrosis of some proximal convoluted renal tubules, but this did not occur in seven other animals or in the newborn and fetuses. There was occasion-

ally necrosis of diaphragmatic, abdominal and spinal muscle fibers, but this was inconstant. The third lesion was occasional crypt cell necrosis of the gut.

Mapharsen (hydrochloride of oxophenarsine or m-amino-p-hydroxyphenyl arsineoxide, Parke, Davis, used immediately after solution).—Nine pregnant mice (13 to 21 days' gestation) and several newborn mice were studied twenty-four hours after injection. Some fetuses in six litters were dead and in these litters there was well-developed neuroblastic necrosis resembling radiation effect. In the newborn mice the necrosis was scant and of outer cortical neuroblasts. Only rarely was there fetal or adult skeletal muscle necrosis. There were no other adult lesions.

Iodoacetate (sodium salt prepared in solution from iodoacetic acid, Eastman).—Six pregnant mice (12 to 21 days' gestation) were studied twenty-four hours after injection. Iodoacetate killed some, and, in one litter, all of the fetuses. It usually made the surviving ones sluggish and slowed the heart beat. None of the fetuses sustained destruction of the nervous system, and skeletal muscle was very rarely damaged in either fetus or adult. In addition, several other pregnant animals were killed by the chemical in less than twenty-four hours, so that it may be concluded that the drug was pressed to the limit so far as acute effects on both fetus and adult are concerned.

Fluoride (sodium fluoride).—Three pregnant mice (13 to 20 days' gestation) showed no lesions twenty-four hours after injection even though several fetuses were dead and two other pregnant animals were killed.

Sequential Blocking.—Potter[11] has designated the use of more than one inhibitor at a time as "sequential blocking." This assumes that each of the inhibitors blocks only at one point. The term is therefore being applied here somewhat loosely for it is likely that chlormercuribenzoate, Mapharsen, etc., may block at several "sulfhydryl points" and thus be sequential blockers.[6, 12] However, each of these agents may have a principal site of action: iodoacetate at lower concentrations is said to act chiefly to inhibit the oxidation of glyceraldehyde 1-3 phosphate to 1-3 diphosphoglyceric acid (phosphoglyceraldehyde dehydrogenase); chlormercuribenzoate affects adenosinetriphosphatase, especially of muscle; Mapharsen may chiefly interfere with pyruvate oxidase. If different types of cells have quantitatively and qualitatively different metabolic pathways, theoretically it would be possible to find a combination of blocking agents that would fit each cell like a key in a lock. At present, this has to be partly rational and partly trial and error. Since neuroblasts seemed to be selectively sensitive to inhibitors of the sulfhydryl system of enzymes, combinations of these were attempted. Some likelihood of success in approaching the selectivity of radiation is ultimately possible, for ionizing radiation does in fact accomplish this highly selective action.

Five pregnant mice (14 to 19 days' gestation) were given 10 mg. per kilogram of Mapharsen and 15 mg. of iodoacetate. This is less than half of each lethal dose and less than a theoretical "summation" of the drugs. No neuroblast necrosis occurred. Two pregnant mice (15 and 18 days' gestation) were given 25 mg. chlormercuribenzoate, 10

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mg. Mapharsen, and 15 mg. of iodoacetate per kilogram. This was just enough to bring about ultimate death of some of the fetuses and to produce neuroblast necrosis in the usual sites for this group of agents. The doses are about half the approximate LD_{50} so that they could "summate" to more than the lethal dose of any one drug. What is especially significant is that they do "summate" and one of them (iodoacetate) is inactive alone.

Placentas.—No lesions were seen that could be considered to have a direct bearing on the action produced by the drugs used. After dinitrophenol the placentas were markedly hyperemic, but in other experiments this was usually not present. When a fetus was autolysed so was the placenta, and in severely necrotized fetuses after TEM the corresponding placentas were hemorrhagic. The use of newborn animals has also helped to rule out direct placental barrier effects in many instances. On the other hand, negative results in some experiments might indicate a barrier effect and also it may change as gestation progresses[13] for the anatomically visible barrier becomes less thick as term is approached.

Histopathologic Remarks.—Necrosis of neuroblasts and other cells—end points used in the acute experiments—have been previously described.[1, 2, 3] It should be noted that occasional necrotic cells throughout the neuraxis occur in all rat and mouse fetuses (based on a large number of controls from 7 days to term). Therefore substantial damage has been the actual criterion and occasional isolated or groups of two or three necrotic cells have been discounted. They are readily distinguished from the occasional hemopoietic cells seen in the developing brain. They have no special distribution but are more likely to be seen in the cingular cortex above the callosum or hippocampus, in the midbrain, in the central cord, and in sensory ganglia. In addition, necrotic cells occur in embryonic muscle, mesenchyme, and subcutaneous tissue. Their significance is unknown.

In no experiments was destructive damage to bone marrow, lymphoid tissue, spleen, thymus, or other hemopoietic cells, seen except in radiation, Aminopterin, TEM, and mustard experiments.

Malformations that can be recognized have thus far been relatively severe, and the most successful ones produced by radiation because of its extraordinarily selective action on neuroblasts. Milder degrees of damage to neuroblasts seem to be "covered up" as the animal develops and it is doubtful whether some slight defects could be determined without extensive cell counts and detailed comparisons with normals. Clustering or rosette formation of cortical and hippocampal neurons and gross and microscopic irregularities of the cerebellar folia can be easily recognized (Figs. 5, 8), but a slight reduction in volume or change in shape of the caudate-putamen-striatum mass due to interruption of the growth of medially placed neuroblasts late in gestation is unlikely to be proved by inspection of routine sections. This difficulty will be important as less severe damage to the developing brain is studied.

Experiments to date have shown no latent effects except anatomic malformations. Gliosis has never developed (injuries seem to have been highly selective), abnormal blood ves-

sels have not been seen, latent degenerative processes that might reflect a biochemical defect acquired at the time of injury have not turned up. Further studies in these areas are in progress.

Histochemical changes in the embryo brain during normal development have not borne directly on these studies as yet. Feulgen, alkaline phosphatase, and glycogen stains on whole fetuses have been performed at various stages with emergence of one interesting fact. The liver does not stain for glycogen (McManus periodic acid Schiff procedure), until very near term. This may in the future bear on the evidently changing metabolism of the more mature neurons toward an adult type of dependence on glucose and oxygen. Clearly the age of the fetus has important relations to its vulnerability to biochemical insults, and expansion of this area of experimentation is needed.

Criteria of Effective Dosage.—The question arises what base line or reference point is used to evaluate the effectiveness of a given agent in destroying neuroblasts, most especially if the agent fails to do so. In the *adult*,[2, 3] the normal was the control and a series of animals was exposed to the particular form of inhibition to a point that just failed to kill them, approximately the LD_{50}. It was demonstrated that between a dose that just fails to damage and one that just kills the whole animal, there is a zone where the cells that are most vulnerable to the particular agent will succumb selectively while the rest of the organism recovers. This zone is so narrow for some agents that selective lesions can practicably be produced only rarely or not at all. With other agents the zone is wide enough, because some cells are more readily injured than the organism as a whole, to obtain selective lesions. Cyanide, insulin, asphyxia have narrow zones but adult brain lesions can experimentally be produced almost at will.[2] Agents such as ionizing radiation and nitrogen mustard operate in a broad zone between lethal and nonlethal effects on the total organism. The variables that may modify and cause enzyme inhibition to deviate from pure chemical reactions when they are applied to the living animal have been discussed elsewhere.[2, 3] By using a battery of agents and comparing them with in vitro studies, useful information can be obtained and the method has become an established one.

In *fetal* studies there are two base lines for acute experiments. The first is the early lethal dose (the LD_{50}) for the parent animal and the second is that for the fetus. The size of the dose, rate of drug absorption and excretion, relative sensitivities of fetus and adult, and especially the duration of action are factors that may determine which will be killed first, but by trial and error with adult sublethal doses, the nearly lethal dose for the fetuses can be determined. Hence, the whole concept of acute inhibitory studies in vivo is based on *relative* differences in metabolism of different tissues. Chronic experiments may be expected to produce somewhat different patterns but they may still indicate relative differences.

DISCUSSION

The *adult* brain depends almost entirely on oxygen and glucose for its energy metabolism and uses about one-fifth of the body's oxygen supply.[14] It stores no appreciable glycogen or other energy reservoirs so it is further de-

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pendent on a continuing blood supply, and is easily injured by lack of glucose or oxygen. It is comparatively resistant to ionizing radiations and agents that simulate them. The anatomic and physiologic variables of blood supply in different parts of the neuraxis have previously been emphasized as prime factors in the selective vulnerability of these parts to injury. Recent work in this laboratory[2, 3] employing the tool of metabolic inhibition in vivo has emphasized that qualitative and quantitative differences of metabolism at various levels and regions of the neuraxis may be of even greater importance. For one example, cyanide, azide, and malononitrile, while selectively damaging cortical, striatal, and other neurons similarly to asphyxia and hypoglycemia, differed sharply from these by also damaging white matter (demyelinization). Though they differ in some respects in pharmacologic and chemical properties, the chief action of cyanide, azide, and malononitrile is believed to be the inhibition of cytochrome oxidase, of which white matter has a meager supply. Apparently white matter depends on aerobic metabolic pathways involving the cytochrome system and the meager supply of oxidase may act as an "enzymatic bottleneck." Such bottlenecks or weak links, in the absence of alternative pathways, may constitute the chief reason why various cells, tissues, and organs may be selectively damaged by different disease-producing agents.

Fetal and *newborn* brain metabolism is in many ways entirely different from the adult. Both fetuses and newborn animals are known to utilize anaerobic pathways for their energy metabolism and to be able to withstand acute episodes of oxygen lack. Himwich[15] has demonstrated physiologically two alternate pathways of energy-yielding metabolism in newborn animals. Normal day-old rats will survive up to an hour in pure nitrogen and can even recover from immersion in water after forty minutes. He found the newborn rats resistant to adult doses of cyanide. Other species showed a comparable resistance to these forms of anoxia although the newborn guinea pig, more mature at birth, is less resistant. When day-old rats are treated with iodoacetate or fluoride they succumb quickly to anoxia, like adults, after only a couple of minutes. Himwich showed that carbohydrate sources, oxidized anaerobically, provided the energy for newborn survival during anoxia, for accumulation of lactic acid occurred in the brain during anoxia but did not in the presence of iodoacetate and fluoride. The source of carbohydrate was presumed to be from other tissues. Histologic sections were not reported so it is not known whether some cells (mature neurons, for example) in the brains of anoxic newborns might have been selectively damaged.

Comparison of Himwich's observations with the experiments being reported here leads to some confirmations, and to some tentative modifications and expansions of our knowledge concerning the developing nervous system. There are differences as well as similarities between fetal and newborn schemes of metabolism. The actively growing neuroblasts in the outer cortex, deep basal masses, brain stem, cerebellar cortex, and dorsal central cord in fetuses of the second half of gestation are characterized by a resistance to acute oxygen lack, to lack of

glucose, to cyanide, and to dinitrophenol (whose action may be to dissociate certain phosphorylating processes from aerobic carbohydrate breakdown). These neuroblasts are extraordinarily and selectively sensitive to the effects of ionizing radiations, whose action in part seems to be inhibition of enzymes with active sulfhydryl groups that are concerned with protein synthesis. These cells are also exceptionally sensitive to nitrogen mustard and triethylene melamine ("TEM"), which are reactive substances that act on sulfhydryl and other prosthetic groups in enzymes.[6] Neuroblasts are also sensitive to some other sulfhydryl reagents: chlormercuribenzoate, iodosobenzoate, and Mapharsen whose actions are probably not limited to any one sulfhydryl enzyme. They are very sensitive to the antimetabolic action of Aminopterin,[16] even more so than are marrow and lymphoid cells. Fluoroacetate, which halts citric acid metabolism and thereby interferes with two- and three-carbon fragment metabolism at the pyruvate level also damages the growing neuroblasts. Plasmocid[3] (which selectively damages adult skeletal and heart muscle and whose action is unknown) also singles out developing neuroblasts. Neuroblasts were not affected by iodoacetate or fluoride; this is of interest for it fits in well with the observations on glucose metabolism in fetuses between the ninth day and near term. In this period the neuroblasts are relatively insensitive to hypoglycemia and at the same time the liver does not store glycogen. As term approaches, however, glycogen appears in the liver and the more mature young neurons become sensitive to a lack of glucose, and after birth, insulin causes necrosis of some neurons similar in pattern to that in the adult. A tentative explanation of these findings includes the likelihood that the fetal brain in this period does not depend so much on glucose as on some other substrates, possibly two- and three-carbon fragments at the pyruvate convergence point. The fluoroacetate effect offers some support for this hypothesis.

The cyanide effect seems at first a paradox but certain observations suggest a possible mechanism. The dorsal spinal cord neurons like some of the deeper cerebral cortical neurons mature ahead of many other cells. The dorsal cord neuroblasts are extremely sensitive to radiation for several days during the middle of gestation even though they are not dividing, but they lose this characteristic toward term.[1] At the same time they tend to become cyanide sensitive. The same holds in part for the anterior cerebrum. It seems possible that the attainment of cyanide sensitivity may indicate a development of the cytochrome enzyme system that characterizes adult tissues although it may be modified by the metabolic capacities established by Himwich[15] for this period of development. It will be interesting in the future to observe whether more prolonged asphyxia than that attempted so far will produce histologic lesions similar to those of cyanide and insulin. Chronic anoxia is known to cause externally visible malformations.[17]

Of special interest is the neuroblast sensitivity to inhibition of sulfhydryl enzymes by a number of agents and to Aminopterin which appears to interrupt a stage or stages of nucleoprotein synthesis.[16] Many enzymes depend on –SH for their activity, either for structural integrity or as suggested by

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Barron[6] they may act as electron transfer catalysts. In any event, the presence of these groups is probably not a chance one and there is increasing evidence that the sulfhydryl enzymes may act as an integrated system in growth and proliferative processes.[18] Certainly they seem to form an essential group for the growth (protein and nucleoprotein synthesis) of normal neuroblasts; and there is suggestive evidence that they have a similar function in some neurogenic tumors but not in others.[19] Thus another characterization is possible, namely, that a system of sulfhydryl enzymes is of especial significance to the rapidly developing embryonic nerve cell.*

The mechanism of malformations of the nervous system that follow metabolic injury, including radiation, seems to be a threefold process: the destruction of building blocks (neuroblasts) by the mechanisms outlined; secondary induction of new patterns of growth such as rosettes, possibly due to nucleic acids liberated during injury; and the timing (critical period) of the injury. Additional variations may be had by varying the type of injury, hypoglycemia, and cyanide, for example. Still another effect to be studied is the possible slowing of growth without actual destruction of cells as seems to occur in the fetal skeleton after radiation.

The relations of these observations and speculations to maldevelopments of the nervous system in general are fairly clear. Through the artificial circumstance of experiment the neuroblast has been shown to be unusually sensitive to interference with its protein synthesis by a variety of means and hence to be a weak spot in the developmental sequence of the nervous system. No questions regarding human maldevelopments (except those caused by radiation) are directly answered but they suggest several possibly fruitful lines of future investigation: common and uncommon viruses, not necessarily neurotropic in the usual sense, that may interfere with nucleic acid synthesis in the vulnerable neuroblast[20]; endocrine imbalances that humorally may influence rapid cellular growth; acute and chronic effects of drugs and medicines alone or in combination; nutritional defects[21]; and further experiments to characterize the developing nervous system biochemically.

*Preliminary experiments in this laboratory have shown that ACTH and cortisone damage neuroblasts in fetuses and newborn animals in a manner similar to sulfhydryl reagents such as chlormercuribenzoate, etc. ACTH not only mimics the sulfhydryl reagents but also damages more mature nerve cells in the newborn, and damages embryonic muscle.

SUMMARY

The developing nervous system in vivo, specifically its neuroblasts, has been found to be unusually susceptible to acute metabolic injury by ionizing radiation, certain sulfhydryl reagents, other inhibitors and antimetabolites. It has been found relatively insensitive to acute interference with glucose and oxygen metabolism except late in development. In the first third of gestation the neural tube is resistant to radiation and possibly other agents but this period is in need of more investigation.

Injuries in the latter two-thirds of gestation cause the development of progressive malformations of the nervous system during growth that carry over into adult life. The most important mechanisms that determine the form of the malformation are the actual destruction of building blocks

(neuroblasts), and the time during gestation (critical period) at which the injury occurs.

These experiments, which were carried out on experimental animals, chiefly rats and mice, invite attention to the possibility that a variety of agents may act during nervous system development to produce malformations.

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SPEECH THERAPY IN CEREBRAL PALSY

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THE interactions of human beings are entirely communicative. Our whole ethicosocioeconomic structure is cemented together by the signalling systems of sound and gesture. Meanings, thought processes, emotions are transmitted by one human being and received by another only over the carrier waves of language.

Language disorders are effective insulating barriers to normal human interactions. An individual with these deviations causes a hiatus in the communicative process. Since these distortions are unusual, a whole series of negative reactions occurs. Almost automatically, a child with aberrant language performance, instead of acceptance by the group, is exposed to an emotional range from sympathy to indifference to rejection, and may be labelled as anything from "idiotic" to "queer."

In the past twenty-five years, the scientific method has been brought to bear upon this serious problem. Objective experimental observations have shown clearly that a particular child with a particular language disorder may indeed be an "idiot," or may indeed be "queer." However, the scientific method has also shown that these labels are only the incidental and occasional effects of failures in the communicative process. If all individuals with language disorders were to be placed in one long line, at either end would be a comparatively few who were actually "idiotic" or "queer." The great mass of the rest could be shown to be potentially "normal," and capable of total integration within modern human culture if proper habilitation were to be available.

The communicative disorders of cerebral palsy are challenging, complex, and intricate. When it is considered that cerebral palsy itself is probably the most frequent of the neuromuscular crippling conditions,[1] and that habilitation of an individual is only complete when he is no longer excluded from human interactions, the importance of exact information on the extent of communicative problems in this condition becomes clear. In 1939, we estimated this incidence as being from 65 to 75 per cent.[2] In 1948, at the request of Dr. Winthrop M. Phelps, a survey made of the rather severe cases at the Children's Rehabilitation Institute showed that 94 per cent had some degree of speech and hearing involvement.[3] In 1950, Wolfe evaluated fifty cases of cerebral palsy and found 70 per cent of the patients had "inadequate articulation."[4]

Information from a much larger series of cases is now available. In 1951, a survey was made of the 1,002 cases of cerebral palsy now living in Kansas who had been examined through the Kansas Crippled Children's Commission, or by the Institute of Logopedics.[5] Seventy-three and two-tenths per cent of the 467 cases giving adequate information for judgment had handicapping disorders of speech and hearing, thus confirming our earlier estimate. Of this group of 467 cases, 22.3 per cent were helpless, and an

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additional 66.0 per cent were seriously handicapped. The speech and hearing disorders were found primarily in these two groups. Convincing evidence of the handicapping nature of communicative disorders is found in the fact that only about one-third of the potentially employable males were actually gainfully employed.

It is quite possible that many of these communicative disorders can be predicted at the time of birth. From the rehabilitative point of view this is extremely important, for the development of overt expression and reception commences at this time. Our experience convinces us that the earlier speech therapy is commenced, the better the eventual results. Advice can and should be given to parents as soon as possible concerning the provision of certain types of procedures which will assist the damaged brain in the management of its communicative environment.

A study completed in 1951 at the Institute of Logopedics gives some hope that this is possible.[6] Wilson reviewed the histories and the clinical reports of the physicians attending the births of 115 infants later developing cerebral palsy with speech disorders. These histories were compared with the histories of the births of 115 "normal" children, selected at random. Among other deviations from the "normal" records was a constellation of difficulties related to maintenance of life in the newborn infant. Table I shows these mathematically significant differences to lie in very large discrepancies in the initiation of breathing with its accompaniments of cyanosis and delayed birth cries, convulsions, paralyses, rigidities, etc., nursing difficulties, food sensitivities, and neonatal jaundice, except erythroblastosis.

In this series of cases, four babies were born with erythroblastosis who later developed cerebral palsy with speech disorders. By mathematical accident, this number is too small for significant predictive value, and it was therefore omitted from Table I. Its clinical significance is well known, however.

TABLE I. BIRTH HISTORIES OF 115 CASES OF CEREBRAL PALSY

	CEREBRAL PALSY (%)	NORMAL CONTROLS (%)
Artificial resuscitation	29.5	7.0
Cyanosis	29.0	2.0
Delayed birth cry	25.3	2.6
Convulsions, paralyses, rigidities, fevers, and other	59.0	0.8
Nursing difficulties (gavage, etc.)	20.5	1.7
Food sensitivities	12.0	None
Neonatal jaundice, except erythroblastosis	20.0	2.6

(All percentage differences are mathematically significant.)

The predictive values of this particular study are extremely interesting. Assuming that artificial resuscitation, cyanosis, and delayed birth cry are essentially related factors, and that the nursing difficulties are essentially related to the convulsions, paralyses, etc., a newborn infant with these two groups of symptoms has only one chance in 170 of normal recovery without a speech disorder. If this same infant has neonatal jaundice in addition, he has only one chance in 1,315. Omitting the respiratory factors leaves the infant still with only one chance in 695, if the other symptoms are present.

Even if this sample should prove to be skewed in later work, it seems clear that parents of a newborn infant showing these constellations should be informed of the probability that their baby will have cerebral palsy with a communicative disorder. At the same time, the first rehabilitative advice should be given, as well as careful medical and psychiatric counsel.

In most instances, however, a child with cerebral palsy comes to the cerebral palsy clinic without such preparation. After medical diagnosis, assignment of modalities of treatment, etc., it becomes the task of the speech therapist to analyze the communicative performance of the patient, and to plan the rehabilitative procedures. No analysis of this process is available in the literature. It was therefore decided that a more or less detailed review of 100 consecutive cases of cerebral palsy with language disorders might prove useful.

The 100 cases to be described are in addition to the 115 studied by Wilson and reported above. Nearly all were classified medically by Dr. Winthrop M. Phelps, and I made all of the language analyses. These factors are therefore quite constant throughout the series.

The patients ranged in age from 2 to 45 years, with an average of 8.7 years. Sixty-three were male, and thirty-seven female. This series is definitely skewed in case type, age, and sex distribution, although cerebral palsy with accompanying speech disorders does occur more frequently in the male.[7] This skewing is the result of the sampling method, and inferences cannot be drawn concerning the relative numbers of the various types of cerebral palsy, age, or sex distributions from this study.

As shown in Table II, all of the patients had rather serious involvements of language. Patients with moderate language disorders include those able to speak and comprehend fairly adequately, but with definite serious handicaps. Patients with severe language disorders include those unable to speak or to comprehend more than a few simple words and sentences. Speechless cases were without language. Echolalia was defined for this series as the repetition of words and phrases without comprehension. The term aphasia needs further explanation: It is probable that the presence of aphasia in a given case can only be satisfactorily delimited by an over-all description of the individual's behavioral peculiarities. These consist of abstracting, categorical disorders, etc. This point of view has been described in former publications.[8] Aphasia in children cannot be accurately delimited on the basis of the specific speech continuity, or the visual or auditory perceptions alone. The

TABLE II. LANGUAGE PERFORMANCE OF 100 CONSECUTIVE CASES OF CEREBRAL PALSY WITH SPEECH DISORDERS

LANGUAGE DISORDER	SPASTIC PARALYSIS 19 CASES	ATHETOSIS 58 CASES	TREMOR 3 CASES	ATAXIA 9 CASES	RIGIDITY 11 CASES	TOTAL
Aphasia	7	7	0	2	3	19
Echolalia	1	2	0	1	2	6
Speechless	7	21	0	4	4	36
Severe	8	17	0	2	1	28
Moderate	7	13	3	1	2	26

proof of this is clinical and pragmatic. For the present, however, the term aphasia in Table II covers a group of cases of cerebral palsy with clear-cut communicative behavioral patterns sufficient to distinguish them from other language disorders, and for whom certain special techniques related to the aberrant patterns seem to be necessary for clinical improvement.

Table II shows that about one-half of the spastic and rigid groups showed these signs, about one-third of the ataxics, and about one-sixth of the athetoids. Range of severity of the handicap is fairly well distributed except for the three tremor patients who were only moderately affected.

In order to provide for rehabilitative planning, it is next necessary to analyze in more detail exactly what portions of the speech mechanisms are responsible for the handicaps shown in Table II.

The structures used for the mechanics of speech are also essential for life. Certain anomalies of function produced by cerebral palsy, and seen in locomotion, grasping, sitting, etc., cannot appear in the speech structures, or death would result. No doubt some of the deaths in early infancy are due to involvement of the speech mechanisms.

One of the important basic processes of the speech mechanics is the neurochemical organization of breathing. Deviations from normal respiratory patterns are limited by the organism's demands for air exchange. In cerebral palsy, breathing disabilities frequently come very close to the limits of life, leaving very little flexibility for the modifications necessary for speech.

The most frequently encountered of the breathing anomalies are shown in Table III. Irregular cycling refers to gross deviations from the normally predictable time and amplitude of the inspiratory-expiratory movements. Shallow breathing is defined as a rather rapid series of low amplitude excursions, coupled with low vital capacity, when measured on the wet spirometer. Thoracic-abdominal opposition occurs when the thorax or the abdomen makes either inspiratory or expiratory excursions while the other is doing the reverse, called by Dr. Phelps "reversed breathing." Stertorous breathing occurs as the result of the halting or impeding of either inspiratory or expiratory movements by spasmodic or tonic occlusions of the airway, most frequently by the radix of the tongue, and the posterior wall of the oropharynx. Nonvolitional breathing cannot be voluntarily modified by the case. Deformities of the thorax comprise most frequently a fairly rigid and sometimes deformed sternum, accompanied by thoracic expansion only in the region of the ninth to twelfth ribs. Usually there is little or no abdominal expansion also. This is felt to be produced by inadequate standing and sitting posture, and by the use of tight chest or belly bands over long periods of time for the purpose of retention of the patient in a chair, particularly in opisthotonus. These deformities have been noted as occurring rather frequently since the beginning of our work at the Institute in 1934.

Table III shows that all classifications of cerebral palsy except the three tremor cases had some anomalies of breathing, but all of the athetoids had such anomalies.

These abnormalities affect the course of speech development in three major ways: (1) In normal children, quiet

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breathing approaches a sinusoidal curve on graphic equipment. When speech is called for, inspiration becomes very rapid, while expiration lengthens into a slow sustained curve. This occurs from the time of the birth cry onward. A child unable to modify the breathing curves in this way lacks one of the main bases for speech. (2) These artifacts are accompanied by insufficient aeration of the lungs over long periods of time, with a consequent intermittent elevation of the CO_2 content of the blood stream, and an intermittent depression of the O_2 level. As a result, the respiratory medullary center becomes hyperirritable intermittently and triggers breathing reactions upon very small exogenous and endogenous stimuli. This initiates a vicious cycle since these overflows can only result in further respiratory irregularities. (3) The tendency toward reduction of the blood O_2 may result in pallor, dullness, slowness of learning, confusions of judgment, irritability, and perhaps certain emotional maladjustments.

Breathing is also subserved by reflex laryngeal function. Deglutition also involves the laryngeal valving reflexes, as do emergency and other major functions of the organism. In 1949, I reported the anomalies of laryngeal function in some detail.[9] Table IV shows their distribution in the 100 consecutive cases. Spasmodic anomalies of constriction and dilation occurred primarily in the athetoid and rigid cases, while errors of flexibility such as pitch and volume deviations were found mainly in the tremor and spastic groups. Errors of confusion and timing were found mostly in athe-

TABLE III. BREATHING ANOMALIES OF 100 CONSECUTIVE CASES OF CEREBRAL PALSY WITH SPEECH DISORDERS

ANOMALY	SPASTIC PARALYSIS 19 CASES	ATHETOSIS 58 CASES	TREMOR 3 CASES	ATAXIA 9 CASES	RIGIDITY 11 CASES	TOTAL
Irregular cycling	3	36	0	1	2	42
Shallow	3	13	0	0	0	16
Thoracic-abdominal opposition	4	9	0	1	1	15
Stertorous	0	3	0	0	1	4
Nonvolitional	0	3	0	0	0	3
Deformed thoracic cage	2	5	0	2	2	11
Totals	12	69	0	4	6	91

TABLE IV. ANOMALIES OF LARYNGEAL FUNCTION IN 100 CONSECUTIVE CASES OF CEREBRAL PALSY WITH SPEECH DISORDERS

ANOMALY	SPASTIC PARALYSIS 19 CASES	ATHETOSIS 58 CASES	TREMOR 3 CASES	ATAXIA 9 CASES	RIGIDITY 11 CASES	TOTAL
Dilator spasm	0	11	0	0	0	11
Constrictor spasm	0	16	0	1	3	20
Ventricular fold spasm	0	3	0	0	0	3
Other spasmodic involvements	1	3	0	0	1	5
Monotones, volume errors, etc.	4	0	3	0	0	7
Out of phase with lips, tongue, etc.	0	7	0	0	1	8
Obtuse thyroid angle	0	2	0	0	0	2
Phonates only with mandible depressed	0	4	0	0	1	5
Athetosis of the vocal folds	0	1	0	0	0	1
Totals	5	47	3	1	6	62

tosis. The problem of the obtuse angle of the juncture of the thyroid cartilage actually lies in hypertonic anomalies of the extrinsic muscles of the larynx. The stretch on the lateral surfaces of the cartilage on each side widens the interarytenoid distance to such an extent that occlusion of the glottis can only be attained with great difficulty. There is consequently loss or severe disability in phonation.

The tongue is a complex structure both neurologically and myologically. With at least twenty-one muscles interdigitating in its structural mass, it is logical to expect that in a neuromuscular disorder a great many anomalies should exist. Table V shows the nature and distribution of the gross functional disturbances of the tongue found in these cases. These consisted of: lateral deviations; failures of the lingual apex to elevate; overt ataxia (overshooting reactions); generally gross, clumsy tongues (smooth, overexpanded structures completely occupying the oral cavity); athetoidal movements (usually of a suck-grope pattern); inert and a f u n c t i o n a l tongues; contracted and small tongues (tongues do not contact molars or incisors); retracted tongues (tongues with radices pulled backward to posterior wall of oropharynx and with the apices about an inch or so from the lower incisors); loss of titrative movements; constantly elevated lingual radix; overt lingual apraxia (failure of any volitional movement that is produced reflexly), etc.

These bizarrities are also distributed according to classification of type of cerebral palsy. Many athetoids had more than one anomaly, and practically all of the rigid cases had anomalous tongue functions. Two of the three tremor patients had such anomalies, and about half of the spastic and ataxic patients. All of these disturbances interfere in one way or another with adequate speech mechanics.

TABLE V. ANOMALIES OF TONGUE FUNCTION IN 100 CONSECUTIVE CASES OF CEREBRAL PALSY WITH SPEECH DISORDERS

ANOMALY	SPASTIC PARALYSIS 19 CASES	ATHETOSIS 58 CASES	TREMOR 3 CASES	ATAXIA 9 CASES	RIGIDITY 11 CASES	TOTAL
Lateral deviation	0	5	0	0	1	6
Apical elevation missing	3	10	0	1	2	16
Ataxic	0	0	0	1	0	1
Gross, clumsy	6	22	0	2	2	32
Athetoidal	1	9	0	0	1	11
Inert	1	5	1	0	1	8
Contracted, small	1	1	1	0	0	3
Retracted	0	7	0	0	0	7
Titractive movements missing	1	3	0	0	1	5
Radix constantly elevates	0	3	0	0	1	4
Apractic	0	3	0	0	1	4
Totals	13	68	2	4	10	97

Movements of the mandible are also frequently deviant in cerebral palsy. Table VI describes the distribution of the specific anomalies. Disturbances here are noted in 80 per cent of the athetoid cases, and are also common in the spastic, ataxic, and rigid types. Analysis of temporomandibular subluxation or "mandibular facet slip" has been made previously.[10] If the jaw cannot be depressed by a simple hinged movement because of various muscular

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contractures of an aberrant sort, regardless of the pattern involved, it is still possible to open the mouth by a compensating pull from the external pterygoids, slipping the mandible from its sockets. The function is slow, clumsy, and interferes with speech. Other disorders found in mandibular elevation and depression are, as shown in Table VI: athetoid movements (constant elevation and depression of an irregular sort); snapping and grinding movements; deformities of the temporomandibular joint (enlargements without subluxation, perhaps from previous dysfunction); slow elevation and depression; constant depression; and constant elevation.

TABLE VI. ANOMALIES OF MANDIBULAR FUNCTION IN 100 CONSECUTIVE CASES OF CEREBRAL PALSY WITH SPEECH DISORDERS

ANOMALY	SPASTIC PARALYSIS 19 CASES	ATHETOSIS 58 CASES	TREMOR 3 CASES	ATAXIA 9 CASES	RIGIDITY 11 CASES	TOTAL
Subluxation temporomandibular joint	6	26	0	2	4	38
Athetoid	0	4	0	0	0	4
Snapping, grinding	0	2	0	0	0	2
Deformity of temporomandibular joint	0	2	0	0	0	2
Slow elevation and depression	2	2	0	0	0	4
Constant depression	2	10	0	0	1	13
Constant elevation	0	1	0	0	0	1
Totals	10	47	0	2	5	64

TABLE VII. ANOMALIES OF THE TEETH AND HARD PALATE IN 100 CONSECUTIVE CASES OF CEREBRAL PALSY WITH SPEECH DISORDERS

ANOMALY	SPASTIC PARALYSIS 19 CASES	ATHETOSIS 58 CASES	TREMOR 3 CASES	ATAXIA 9 CASES	RIGIDITY 11 CASES	TOTAL
Severe dental caries	0	0	0	0	1	1
Enamel defects	0	0	0	1	0	1
Retracted incisors	0	1	0	0	0	1
Overshot jaw	1	12	0	0	0	13
Undershot jaw	0	1	0	0	1	2
Medial open bite	2	4	0	0	0	6
Lower dental circle pointed	0	0	0	0	1	1
High, narrow palate	1	6	1	0	0	8
Flat, wide palate	1	1	0	0	0	2
Totals	5	25	1	1	3	35

Structural anomalies of the teeth and hard palate were also quite frequent in this series, as shown in Table VII. It is generally accepted that these abnormalities delay, or prevent, the normal development of speech.[11] Over one-third of the cases showed such anomalies. Some of these may be due to faults in embryonic development, others are no doubt the result of chronic disturbances of pressure from the tongue and cheek muscles. These deviations were more frequent in the athetoid cases, particularly the orthodontic malformations: retracted incisors, overshot and undershot jaws, flat and high narrow palates.

Table VIII shows that about one-fourth of the patients have various disturbances of coordination of the musculatures of the cheeks and mouth. Eighty-five per cent of these deviations were found in athetoids, with the remainder occurring in the spastic group.

There are probably many more such dyscoordinations in these cases; the ones counted were evident and gross. They consisted of: contractures of the platysma; general facial grimaces; bizarre lip closing and opening (various compensatory muscles utilized, e.g., "purse-string closure" by means of the orbicularis oris acting alone); various cheek muscles afunctional (portions of the buccinators were frequently flaccid); athetosis of the cheeks (constant irregular movement); kinesthetic confusions of the tongue and lips (movement of one when the other was volitionally intended). All of these interfere with the speech mechanics.

In a number of instances there were anomalies of contracture of the neck musculature, particularly those muscles involving the speech process. While they are probably also involved, analysis of the scalene and other cervical muscles was not made for this study. Table IX shows the gross involvements found, consisting of: contracture of various suprahyoids, contracture of various infrahyoids; contracture of the sternocleidomastoideus; flaccidity of the trapezius; general athetosis. The incidence in this series is probably too low; other experience shows a greater number of problems of this sort.

TABLE VIII. ANOMALIES OF FACIAL FUNCTION IN 100 CONSECUTIVE CASES OF CEREBRAL PALSY WITH SPEECH DISORDERS

ANOMALY	SPASTIC PARALYSIS 19 CASES	ATHETOSIS 58 CASES	TREMOR 3 CASES	ATAXIA 9 CASES	RIGIDITY 11 CASES	TOTAL
Contracture of platysma	1	4	0	0	0	5
General facial grimace	0	2	0	0	0	2
Bizarre lip closing and opening	3	9	0	0	0	12
Various cheek muscles afunctional	0	4	0	0	0	4
Athetosis of the cheeks	0	2	0	0	0	2
Kinesthetic confusions of the tongue and lips	0	1	0	0	0	1
Totals	4	22	0	0	0	26

TABLE IX. ANOMALIES OF THE NECK REGION IN 100 CASES OF CEREBRAL PALSY WITH SPEECH DISORDERS

ANOMALY	SPASTIC PARALYSIS 19 CASES	ATHETOSIS 58 CASES	TREMOR 3 CASES	ATAXIA 9 CASES	RIGIDITY 11 CASES	TOTAL
Suprahyoid contracture	1	1	0	0	0	2
Infrahyoid contracture	0	5	0	0	0	5
Sternocleidomastoideus contracture	1	7	0	0	1	9
Trapezius flaccid	0	1	0	0	0	1
General athetosis	0	1	0	0	0	1
Totals	2	15	0	0	1	18

The next analysis is exceedingly important for comprehension of the reasons for the failure of the speech stereotypes to develop in many cases of cerebral palsy. Table X shows that all but two cases of the series had some difficulty in the chewing, sucking, and swallowing reflexes. These two cases were both echolalic. Since the speech stereotypes emerge directly from these vegetative orientations, the relationship is clear. In Table X the term

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"generally abnormal" refers to all sorts of deviant patterns, irregularities in coordination, etc. For example, push-pull patterns of tongue movement are very common. The anomalies of swallowing separated from this general picture consist of regurgitations, interferences of the swallowing waves by fortuitous, out-of-phase sucking reflexes, etc. Drooling is a frequently distressing condition in these children, which may be more common than is shown by this series. The presence of drooling, however, gives incontrovertible evidence that the sucking and swallowing reflexes are abnormal.

The material thus far reported in Tables III through X is sufficient to account for a great deal of the speech disabilities of these patients. Speech, however, is also a learned act, and a receptive as well as transmitting process. Normally, coordinated vision is an essential part of the development of speech. Large-scale information on the importance of vision in the process was given by Noeller at the Institute of Logopedies in 1948.[12] A study of 5,034 visually handicapped children showed that 11.1 per cent had speech disorders, an incidence over twice that of the normal population. Table XI shows the gross visual disorders present except acuity which was not measured in this series. These consisted of: nystagmus; strabismus; tic; shifting dominant field (an extremely bewildering and frustrating phenomenon for the child); agnosia (lack of recognition of objects presented visually, which are recognized by other sensory fields); doubtful perception; loss of upward movement of the eyeballs (in athetoids only). Twenty-six per cent of the patients had some difficulty with the visual apparatus, in addition to the acuity problems that no doubt existed.

Finally, the question of hearing losses is critical for the development of normal speech. The cases reported in Table XII are only those gross losses easily demonstrated by tuning

TABLE X. DEVIATIONS FROM NORMAL PATTERNS OF THE CHEWING, SUCKING, AND SWALLOWING REFLEXES IN 100 CONSECUTIVE CASES OF CEREBRAL PALSY WITH SPEECH DISORDERS

DEVIATION	SPASTIC PARALYSIS 19 CASES	ATHETOSIS 58 CASES	TREMOR 3 CASES	ATAXIA 9 CASES	RIGIDITY 11 CASES	TOTAL
Generally abnormal	15	45	2	7	8	77
Anomalies of swallowing	1	4	0	1	0	6
Drooling	2	10	2	1	2	17
Totals	18	59	4	9	10	100

TABLE XI. ANOMALIES OF THE EYES (EXCEPT ACUITY) IN 100 CASES OF CEREBRAL PALSY WITH SPEECH DISORDERS

ANOMALY	SPASTIC PARALYSIS 19 CASES	ATHETOSIS 58 CASES	TREMOR 3 CASES	ATAXIA 9 CASES	RIGIDITY 11 CASES	TOTAL
Nystagmus	2	1	0	1	0	4
Strabismus	2	3	0	0	0	5
Tic	1	0	0	0	0	1
Shifting dominant field	2	5	0	0	1	8
Agnosia	0	0	0	0	1	1
Perception doubtful	2	1	0	0	1	4
Loss of upward movement	0	3	0	0	0	3
Totals	9	13	0	1	3	26

fork and watch tests. Such losses were present in all classifications except the three tremor cases. The fact that such losses existed in 25 per cent of the case series is rather interesting. This is from three to four times the incidence in the normal population. If routine audiometric testing had been done on all cases, the incidence would have been considerably higher. The distribution in the deaf and Rh athetoids has also been separated because of its particular interest in classification.

ways as soon as the normal time for the development of the first communication has passed without such development. This can be set arbitrarily at one year of age, although we have commenced with a number of children before this time.

The problems coming to attention can be conveniently analyzed under four general heads: (1) Highly variant neuromuscular dysfunctions of the respiratory, laryngeal, and chewing, sucking, and swallowing mechanisms. These disabilities alter their character-

TABLE XII. GROSS LOSSES OF HEARING IN 100 CONSECUTIVE CASES OF CEREBRAL PALSY WITH SPEECH DISORDERS

TYPE	NUMBER OF CASES	NUMBER OF CASES WITH LOSS
Spastic paralysis	19	3
Athetosis	58	16
Deaf and Rh athetoids	9	9
Arm and neck athetoids	2	1
Tremor	3	0
Ataxia	9	3
Rigidity	11	3
Totals	100	25

DISCUSSION

The above description of 100 consecutive cases of cerebral palsy with speech disorders shows rather clearly the task of the speech therapist in the cerebral palsy clinic. The habilitation program must be undertaken on an individual basis with each case, and with a thorough understanding of the problem. Only the speech therapist with the most thorough training can possibly do adequate work in this condition.

The range of language disorders is from complete loss of communicative ability to moderately severe disorders. It is the task of the speech therapist to erect as nearly normal language as the limitations of the patient and available knowledge permit. Such work commences ideally with the birth of the child with cerebral palsy, and al-

istics as they are produced on the basis of spasticity, athetosis, ataxia, tremor, or rigidity, and must be approached differently as these different conditions exist. (2) Visuoauditory disabilities of central and peripheral origin. (3) Aphasic and dysphasic communicative behavioral reactions. (4) True mental deficiency.

If only the first three categories are considered, is rehabilitation merely wishful thinking, or can it be objectively measured without emotional coloration? That it *can* be objectively evaluated and scored was shown by Berko in a recently completed study using Institute of Logopedics cases.[13] Without recourse to the opinions of the speech therapists, occupational therapists, physical therapists, physicians, teachers, official records, etc., Berko studied forty-six cases of cere-

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bral palsy for an average of 0.44 year. During this time the average measured gain on the Vineland Social Maturity Scale was 0.68 year, or one and one-half times the gain to be expected from ordinary chronological maturation. An adequate program for cerebral palsy *does* produce gains, and these gains *can* be objectively measured.

An adequate program for speech therapy not only provides for individual work on an individual case basis by a properly trained speech therapist (such training may be defined arbitrarily as a minimum of forty-two semester hours in the field of speech therapy, plus special training in neurophysiology, cerebral palsy, and aphasia), but also takes recognition of the fact that these communicative disorders exist not only in isolated structures such as the tongue, but in the structural and experiential totality of the child. A rehabilitative program of a proper sort must not only be fitted to the organic underlay of the condition, but to the child's whole social, economic, and ethical milieu.

With this approach, counselling with parents becomes as important a portion of the program as the actual therapy, or, for example, the provision of religious experience is no less demanded than the rearrangement of the respiratory patterns. Medical care leading to an optimum state of health is no less needed than adequate psychological measurement and advice: in short, because of the totalizing nature of the handicap, attention must be paid to *the child* with cerebral palsy, rather than only to the *cerebral palsy* the child has.

It is regretted that the limitations of time and space do not permit a similarly detailed analysis of modern rehabilitative details, the use of the Miller kymograph, for example, and other graphic equipment. The approach is quite objective, and rather successful, even though complete normalcy is very seldom attained. In any event, it is possible, utilizing the sort of analysis presented here, to work clearly, and rather well, in the direction of giving these children a basis for life in this speaking world.

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Psychologic Aspects of Pediatrics

THE INTEGRATED TREATMENT OF A YOUNG CHILD WITH A SPEECH DISORDER*

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INTRODUCTION

THIS report is designed to illustrate integrated therapy for a young child with a speech disorder. The steps in this treatment consists of (1) establishing a friendly relation with the child, (2) specific procedures to correct the defective speech, (3) combating undesirable parental attitudes, and (4) treatment of the child's own disturbed state.

The various devices which are used to train a child to correct a speech defect, attractive and amusing as they may be, are not in themselves sufficient to effect a cure. They are effective only insofar as they are made acceptable to the patient. In the case presented here the important factor is the permissive and consistent attitude of the therapist, which enables the child to accept corrective speech suggestions. The sympathetic relationship established between the therapist and the child helps the latter to relinquish devices for securing attention and to accept the necessity of behaving on his own age level, thus strengthening him in the process of growing up.

CASE HISTORY

Bobby was first sent to the therapist at the age of 4 years, because of a severe dyslalia, a form of unintelligible speech commonly known as baby talk. He was a well-developed boy, the youngest of three children. His brother was three years older than he and his sister four years older. He was born at term. There were no serious illnesses which might account for his speech defect. Teething was normal. He started to walk at about 16 months. He had a normal babbling period and said his first words "mama," "dada" at 13 months. His first sentences were spoken when he was 2 years old.

Bobby was ambidextrous. His handedness tests showed mixed dominance with 65 per cent right to 35 per cent left-handed responses. He had superior intelligence; his I.Q. on the revised Stanford-Binet was over 135.

In the family background appear the following language deviations: The father's brother stuttered severely. Both Bobby's mother and brother had difficulty in learning to read. The brother was left-handed.

Bobby's father was a detached individual, who played a rather passive role in the education of his children. The mother was a rigid, perfectionistic person.

The defective articulation (dyslalia) was considered a motor speech delay on a constitutional basis. Certain consonants, f, v, k, g, th, sh, s, l, were imperfectly articulated. K and

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g were generally substituted by t, and all final consonants were omitted. Bobby talked r a p i d l y, his words tumbling over each other (cluttering).

Specific Procedures in Speech Correction.—Bobby was seen three times weekly for forty-five-minute sessions. In an effort to establish a friendly relation, many games and toys were made available and he was encouraged to choose freely. Among these were construction games, lottos, crayons, clay, paints, and the like. At the beginning he picked but one game, picture dominoes. He insisted that the unused dominoes be arranged in exactly the same way each time. He was equally insistent that the therapist turn on the lamp by the window, while he, himself, turned on the one by the door. His anxiety was too great to allow him to enter a new situation such as trying new games. He had absorbed his mother's rigidity and perfectionistic standards, which interfered with his doing anything he had not done before.

Bobby sensed his mother's great concern about his speech and wanted very much to live up to her high standards. Since he felt unable to do so he avoided many speech situations or used e v a s i o n s, saying "don't know," or asking his nurse to answer questions for him.

He was not ready to accept any direct reminders of his speech defect, and consequently the first attempts at speech correction had to be indirect.

At the very beginning of treatment it was the therapist's task to understand and to communicate to the child the meaning of his mother's attitude toward his speech difficulties. The discrepancy between his high standards and his inability to live up to them was a constant source of anxiety and conflict. So at this point the cooperation of the mother was called for. She was frequently assured that the boy could be helped best if his speech defect were completely ignored at home. The mother cooperated to the best of her ability at home, with the result that the boy was less defensive about his speech. His friendship with the therapist developed sufficiently so that it seemed safe to start a carefully planned indirect speech correction.

This took the form of the introduction of an imaginary figure called "Peter," a frequently used device with children, reversing the teacher-child role. It proved effective with Bobby. Bobby was shown the picture of a little boy slightly younger than himself and was told that this was Peter and that Peter had a hard time saying words which began with k.

Though we generally start with a lip sound, which the child can see being made and can therefore imitate like f or v, in this case advantage was taken of the fact that k was already correctly articulated sometimes and therefore the easiest sound for him to learn.

The actual articulation of k was preceded by first establishing a proper auditory picture, a procedure that is used for every sound to be corrected. As one of the auditory exercises for the sound k, a story was read to Bobby in which words beginning with k were exaggerated by tone of voice. A picture card was shown and Bobby was asked to put a chocolate bean on the pictures of words beginning with k. At another visit, when the therapist read to him, he

tapped her on the shoulder or rang a bell when he heard the sound of an initial k.

Only after Bobby's auditory picture of k was established did he demonstrate to "Peter" how to articulate the k. Bobby was told that he would make it easier for "Peter" to learn the k if he pressed down the tip of his own tongue with a lollypop.

Bobby cooperated fairly well during the sessions when he instructed "Peter" how to articulate the k, and he enjoyed himself thoroughly with games which followed the mastery of the isolated k and g. For example, a picture of a candy store was shown to him. It was used as a model in making a candy counter on top of the table. Bobby liked both being a salesman praising the good candy and the customer buying it. Another game which intrigued Bobby was the "catch game." Whenever he caught more than one of the marbles being rolled to him, he would yell "Catch."

For variety a toy train was used. Each time the green signal was flashed Bobby shouted "Go." Another time the therapist and he put on their hats and pretended to go visiting. They praised the good cake served to them and they drank "good coffee" or "cocoa" with relish. Stories were read and the therapist stopped before words with initial k's and g's to give Bobby a chance to repeat them.

After two months Bobby employed the k and g properly and was happy to talk into the recording machine. Prior to this no record was taken of Bobby's speech because of his sensitivity toward any speech test situation. He clutched the record to himself all the way home and played it to his family.

The next sound attacked was f, a lip sound that can be seen and usually does not present many difficulties for correction. When Bobby discovered that an additional demand was being made on him, his speech regressed. Cooperation lagged, he cuddled more and frequently asked for his original one-game picture dominoes. Treatment was complicated by the fact that he missed two weeks because of illness. While he was sick at home he was babied. At times he became quite aggressive. He often accused the therapist of giving him a headache, being a "meanie," and told her he hated her and hated to come. All this time it was made clear to him that the therapist's friendship for him remained unchanged. She sympathized with him, ignored his accusations, and demonstrated more affection.

Throughout the period of regression, which lasted about two weeks, no attempt at speech training was made. Instead he was permitted to play with whatever games he liked or just to nestle on the therapist's lap. Thus he went through a very reassuring phase in his friendship with the therapist. Finally the day came when he said to the therapist "Bring me Peter."

With more zest than before, he imitated the f and passed it over to "Peter." Once the sound was established, several f games were employed. To name a few: Bobby's interest for fires and everything connected with them became the basis for a fire department game. Equipped with a helmet, he called orders into a microphone: Fire, Fire, Fire, Fire-engine ready, Fire-engine out, and so on. In this way he was not un-

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pleasantly aware that he was being drilled.

Bobby liked going on fishing trips. He and the therapist used a magnetic fishing rod and rubber fish with irons in their mouths. To increase the amount of practice, pictures of words beginning with f were taped to the fish and Bobby, the successful fisherman, was glad to say what he had caught.

To cope with Bobby's restlessness and at the same time to diminish emphasis on speech, he was given either clay, crayons, or scissors, while the therapist gave him speech exercises in the form of a story.

Bobby's skill with scissors came in very handy when he started a scrapbook to introduce the articulation of s. He was guided into selecting pictures which all began with the sound s. Meanwhile, he was being carefully instructed in the enunciation of s. Later on, to reinforce the s blends, hide-and-seek games were played. The therapist was supposed to close her eyes and the child happily reported the results of his search: a number of picture illustrations beginning with s blends.

While Bobby was able to produce most of the sounds correctly, the isolated sound as well as in words and short sentences, the carry-over outside the office was very poor. The mother's anxiety increased again and she did not control her distress about Bobby's speech when he talked to her. This in turn created new difficulties for Bobby and recurrent regressions. Efforts were made again to dispel some of the mother's anxieties about Bobby's speech. Moreover, favorable reports from the kindergarten about his improvement in speech were referred to Bobby's home. Finally, the mother began to believe that ultimate success was indeed possible. Bobby sensed her renewed confidence and this gave him more courage to speak up at home.

At this juncture Bobby was ready to shoulder more responsibility, and he started to work on the pronunciation of final consonants. When a story was read and he noticed that the therapist omitted a final consonant, he gloatingly rang a bell.

In addition to auditory recalls, Bobby was given exercises in sound discrimination between s and sh, ch, j, z and ch. His ability to repeat nonsense syllables increased from three to six syllables. The repetition of non-sense syllables is given to all children with poor auditory memories in order to strengthen them.

Smooth production of the s blends like sm, sn, sp, sk, st, str, spl, etc. remained a stumbling block, as it frequently does. Some of the necessary drill was given through the medium of a popular game, "Movies." The room was darkened and Bobby named the s blend pictures as he illuminated them by a flashlight.

DISCUSSION

Some of the factors described in the preceding case of a severe dyslalia are typical for children with a motor speech delay on a constitutional basis. The family history usually discloses evidences of language disability. Furthermore the speech-defective child often shows a delay in the establishment of functional superiority of one hand over the other. An investigation of the entire behavior pattern of "baby talkers" usually shows many more immature mani-

festations than just faulty speech, all of which have to be analyzed by the therapist.

In addition, the child's position in the family constellation has to be considered. The fact that Bobby was the youngest of three children probably added to the mother's oversolicitous attitude. We often find among parents an oversensitivity toward their children's speech if the latter show a low resistance in the language area. It is just as common for the children to sense in their parents an overwatchfulness toward their speech defects and many children react the way Bobby did, with frequent speech evasions and fear of meeting new people and new situations.

In Bobby's case the mother's cooperation was enlisted in the very beginning of treatment and it was repeatedly suggested to her that the boy could be helped best if his speech defect could be completely ignored at home.

Since the factors responsible for dyslalia are complex, symptomatic treatment alone is insufficient. The elements of speech training must be integrated into the framework of an all-around remedial approach based on a constructive therapist-child relationship.

Bobby's speech defect probably served him as the most suitable vehicle to express his conflict about growing up and living up to his mother's perfectionistic standards. A warm and solid relationship with the therapist gave Bobby sufficient gratifications to alleviate the growing-up process as well as the appropriate tools for a better management of his speech.

SUMMARY

1. The remedial approach to a speech defect in a boy 4 years of age is described.

2. Treatment to be effective must include not merely speech training but attention to improper parental attitudes and to the child's own reaction to his defect as well.

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Comments on Current Literature

CONGENITAL DERMAL SINUS COMMUNICATING WITH THE CENTRAL NERVOUS SYSTEM OR WITH THE MENINGES

THE *British Medical Journal* for Dec. 29, 1951, carries an informative report of a fatal case of meningitis associated with congenital dermal sinus. The authors, B. S. Cardell and Bernard Laurance,[1] discuss from a practical point of view the clinical and pathologic aspects of congenital dermal sinus as a rather rare, but preventable, cause of serious infection of the central nervous system, or its coverings. They review the salient features of the cases recorded previously, and add a carefully studied case of their own.

A congenital dermal sinus "consists of an epithelial tube extending inwards from the skin of the midline of the back to connect with the central nervous system or its coverings." Histologically the lesion is identical with the pilonidal sinus, which occurs in the sacrococcygeal region and has no communication with the spinal cord or the meninges, but differs from the pilonidal sinus in that the dermal sinus may occur at any site between the occiput and the sacrococcygeal region, and is connected with the central nervous system or the meninges. An analysis of cases reported in the literature showed the following site incidence: cranial (occiput), two; cervical, one; thoracic, nine; lumbar, ten; sacral, twelve; sacrococcygeal, one. The majority of the cases has been shown to be associated with other developmental anomalies such as spina bifida occulta and cranium bifidum.

In considering the pathogenesis of this condition the authors favor the explanation of Walker and Bucy[2] that a dermal sinus can occur at various levels of the spinal cord, and is due to a failure of the neural crest ectoderm to separate from the cutaneous epithelial ectoderm at the site of the deformity. According to this view, the associated abnormalities of the vertebral column, spina bifida, and cranium bifidum, as well as extension of the spinal cord into the sacrum, may be accounted for by the presence of dermal inclusions which tend to disturb the formation of the vertebral column and prevent the normal dedifferentiation of the coccygeal segment of the spinal cord into the filum terminale.

The case of their own, which the authors report in detail, is that of a male child, 2½ years of age, who complained of pain in the sacral region at the site of "a red spot," which the parents had noted since birth. Apparently the primary episode occurred at the age of 19 months, seven months before admission to the hospital. The lesion which had been discharging purulent material seemed to heal spontaneously, but reappeared twice during the fortnight following its initial appearance. Three days before admission to the hospital the child complained again of pain in the sacrococcygeal region. At the time of admission the patient was acutely ill,

presenting all the characteristic manifestations of meningitis. On physical examination a slightly hairy, red area was observed at the level of the second and third sacral vertebrae, but no evidence of discharge was reported at this time, and no sinus was noted. A lumbar puncture yielded extremely thick purulent fluid from which a strain of *Staphylococcus aureus* was cultured. The patient expired within twelve hours after admission to the hospital.

At the time of necropsy a minute cutaneous depression surrounded by a tuft of hair was noted just below the level of the second sacral tubercle. From this dimple a spinal tract was observed which could be traced upward through the dura to join the dorsal surface of the spinal cord at the level of the second sacral vertebra. Thick purulent exudate extended throughout the entire spinal subarachnoid space. *Staph. aureus* was cultured from this exudate.

A study of serial sections verified the observations made grossly, and revealed a tract of minute lumen-size extending from the surface of the skin through the meningeal coverings, and communicating with the subarachnoid space. It was obvious that the subarachnoid exudate was maximal at the caudal end of the spinal theca, which suggests that the infection had gained entrance to the central nervous system by way of the dermal sinus. From the nasopharynx of this patient a penicillin-resistant strain of *Staph. aureus* was isolated which proved to be identical with that recovered from the meningeal exudate. It is possible that the organism which invaded the central nervous system may have originated from the child's nose and throat.

The authors conclude that in the case which they report, spina bifida and extension of the spinal cord into the sacral canal were anomalies associated with the dermal sinus, and that their patient developed staphylococcal meningitis as a result of the open dermal sinus, the infection having progressed in all probability from the skin through the sinus tract and into the central nervous system.

In summary, the practical clinical point is emphasized that all dermal sinuses at or above the sacral level should be excised, preferably before infection occurs. The dermal sinus may be very small and its communication to the outside by way of a minute lumen. Consequently any dimpling, localized redness, or any unusual tufts of hair occurring in the midline along the spinal column, should be scrutinized with care in order to detect the possible presence of a dermal sinus.

While infection by way of a dermal sinus may be regarded as an uncommon cause of meningitis, the value of prevention by proper surgical intervention in those few cases seems obvious. Perhaps associated spina bifida or other congenital anomalies of the spine may be of some help in drawing the attention of clinicians to the presence of a dermal sinus.

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News and Notes

The following were certified by the **American Board of Pediatrics** at the examination at New York City, Feb. 1, 2, and 3, 1952.

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Dr. Crosby Ball Deacon, 452 Main St., East, Hamilton, Ontario, Canada.
Dr. Oliver Francis Deen, Jr., 442 W. Lafayette, Tampa, Fla.
Dr. Helmut Max Dehn, 69½ Front St., Berea, Ohio.
Dr. Murdina MacFarquhar Desmond, 2414 Smith St., Houston, Texas.
Dr. Evelyn Edith Dresner, 205 Park St., Ridgefield Park, N. J.
Dr. Harry McCreary Edwards, 207 Todd Bldg., Ocalo, Fla.
Dr. Joseph W. Falcone, 228 Lincoln Rd., Brooklyn 25, N. Y.
Dr. William J. Farley, 624 Mt. Prospect Ave., Newark, N. J.
Dr. Elaine G. Fichter, Dept. of Pediatrics, Louisiana State Univ. School of Med., New Orleans, La.
Dr. Thomas F. Fletcher, Jr., 6600 Medical Group, APO 862, c/o PM, New York, N. Y.
Dr. John R. Ford, 268 N. Main, Gloversville, N. Y.
Dr. Paul C. Gaffney, Children's Hospital, Pittsburgh 13, Pa.
Dr. Michael L. Gilbert, 221 Middle Neck Rd., Great Neck, L. I., N. Y.
Dr. Rodman Gilder, Jr., 1225 Park Ave., New York 28, N. Y.
Dr. John Horace Githens, Jr., 2559 S. Franklin St., Denver, Colo.
Dr. David Goldberg, 269 Forest Ave., Park Forest, Ill.
Dr. H. Samson Gordon, 432 Roslyn Pl., Chicago, Ill.
Dr. Milton Gordon, 34 Dewey St., Huntington, L. I., N. Y.
Dr. Theodore B. Greenfield, 231 Main St., Brockton, Mass.
Dr. Grace Stollar Gregg, 430 Devonshire St., Pittsburgh 13, Pa.
Dr. Norman Albert Harvey, 4 Ackley St., Glens Falls, N. Y.
Dr. Robert H. High, 2600 N. Lawrence St., Philadelphia 33, Pa.
Dr. Sumner H. Hoffman, 193 Garden St., Needham, Mass.
Dr. Louis E. Imperiale, 1638 60th St., Brooklyn 4, N. Y.
Dr. Ethel L. Johnson, Apt. F 3, 144-50 38th Ave., Flushing 54, N. Y.
Dr. Howard A. Joos, 95 Arvin Heights, Rochester 11, N. Y.
Dr. William Everett King, 75-26 Furmanville Ave., Middle Village, L. I., N. Y.
Dr. Lawrence C. Kingsland, Jr., Quarters "O," USN Hospital, Camp Lejeune, N. C.
Dr. Henry Leonard, 112 82nd Ave., Kew Gardens 15, N. Y.
Dr. James G. Lione, 83-10 35th Ave., Jackson Heights, N. Y.
Dr. Donald Emerson McLean, 31 Church St., Winchester, Mass.
Dr. Richard S. Meltzer, 300 S. Goodman St., Rochester 7, N. Y.
Dr. Gerald Miller, Strong Memorial Hospital, Rochester, N. Y.
Dr. Joseph B. Miller, 904 Dauphin St., Mobile, Ala.
Dr. Ruth Avers Miller, 466 Rockaway Ave., Valley Stream, N. Y.
Dr. Virginia Connolly Mitty, 318 E. 19th St., New York 3, N. Y.
Dr. Abraham Nathan, 614 Cortelyou Rd., Brooklyn 18, N. Y.
Dr. Anthony C. Nolke, 5224 St. Antoine, Detroit, Mich.
Dr. W. Frederick O'Connell, 21 Roxborough Rd., Rochester 19, N. Y.
Dr. Albert L. Patrick, 16 Markham Pl., Staten Island, N. Y.
Dr. William Pfeffer, Jr., 300 Longwood Ave., Boston, Mass.
Dr. George Edward Porter, 28 Bank Row, Pittsfield, Mass.
Dr. Dane G. Prugh, 300 Longwood Ave., Boston, Mass.
Dr. John Alfred Ripp, 655 Westbury Ave., Westbury, N. Y.

Dr. Peter Roody, 110 Primrose Dr., New Hyde Park, L. I., N. Y.
Dr. Ira Maurice Rosenthal, 607 Avenue C, Brooklyn 18, N. Y.
Dr. Morton Schaffran, 12 Fox St., Aurora, Ill.
Dr. Jack J. Schwartz, 60 S. Munn Ave., East Orange, N. J.
Dr. Milton Philip Shoob, 212-04 73rd Ave., Bayside, L. I., N. Y.
Dr. William Henry Smith, 51 Bedford Rd., Katonah, N. Y.
Dr. Gerald Solomons, Charles V. Chapin Hospital, Providence 8, R. I.
Dr. Mary Elizabeth Steinheimer, U. S. Army Hospital, Ft. George G. Meade, Md.
Dr. Carter Stilson, 309 Edwards St., New Haven, Conn.
Dr. Avron Y. Sweet, Mt. Sinai Hospital, 5th Ave. and 100th St., New York 29, N. Y.
Dr. Rudolf Toch, 20th Station Hospital, APO 407, c/o PM, New York, N. Y.
Dr. Louis Ira Tyler, Jr., 6820 Goodwood Ave., Baton Rouge 6, La.
Dr. Frank Conrad Vogt, 557 79th St., Brooklyn 9, N. Y.
Dr. Hermann Vollmer, 25 Central Park West, New York, N. Y.
Dr. John Watchko, Indiana Theatre Bldg., Indiana, Pa.
Dr. Walter Brown Watson, U. S. Army Hospital, Ft. Hamilton, Brooklyn 9, N. Y.
Dr. Leo F. J. Wilking, Jr., 161 E. 62nd St., New York 21, N. Y.
Dr. Virginia Nichols Wilking, 161 E. 62nd St., New York 21, N. Y.
Dr. William Martin Wiseman, 1942 Stuart St., Brooklyn 29, N. Y.

The next examination will be at Washington, D. C., May 2, 3, and 4, 1952.

On April 12, 1952, the Pediatric Clinic at Berne, Switzerland, will celebrate the 65th birthday of its chief, **Prof. Dr. Glanzmann.** Prof. Glanzmann is well known to American pediatricians through his pediatric textbook, and his numerous contributions in the field of hematology. The JOURNAL extends its felicitations.

On Feb. 18, 1952, the **Michael Reese Hospital** opened a Child Care Unit in the Institute for Psychosomatic and Psychiatric Research and Training. This unit is intended for the care of all phases of psychiatric and psychosomatic problems in children. Children, approximately between the ages of 6 and 12 years, will be accepted for observation, diagnosis, and evaluation and for short- or long-term therapy. The children will be offered the benefit of psychiatric, pediatric, psychologic, electroencephalographic, and other laboratory facilities for diagnosis. Specially trained personnel in the nursing, occupational therapy, and teaching specialties are available as auxiliary therapists.

Beds are available for private patients of recognized psychiatrists who will be in complete charge of their patients. These psychiatrists will have the use of play therapy rooms and the full cooperation of the resident and full-time auxiliary staff of the unit. Psychosomatic patients must be under the joint care of a pediatrician and a child psychiatrist.

An immediate opening for a fellow in pediatric cardiology is now available in the children's division of Cook County Hospital. Training in angiocardiography and catheterization if desired. For further details, communicate with: Dr. Benjamin M. Gasul, 700 S. Wood St., Cook County Children's Hospital, Chicago, Ill.

Book Reviews

Going to the Hospital. Prepared by The Child Development Center, Children's Hospital of the East Bay, Oakland, Calif., 1951.

This is one of the most clever booklets that has ever come across the editor's desk, and we believe will be found among the most useful. It is simply a drawing book to be given to children a few days before they go to the hospital for a tonsillectomy, with the purpose of preparing the child for the experience. It is a small booklet, 8 by 10 inches, with nine pages of exceedingly good outline drawings by Mildred Bronson to be colored by the child. If something similar has been done before, and is in use in other institutions, it has not come to our attention. It is so simple and psychologically sound one wonders why someone has not thought of it before.

The first drawing to be colored finds the child back in bed at home relating his hos-

pital experience to a playmate. This is excellent psychology as the child is impressed at the very beginning that he is coming back to his own home and will not be left at the hospital. In the next seven drawings the hospital experience is told. The first two show him in the hospital waiting room with his mother, where a "funny shirt" has been put on. The third sees him leaving his mother and going upstairs with the nurse. Thus he is prepared for the separation from the parents that takes place and which so frequently produces emotional outbreaks and upsets. In the fourth he is in the operating room where he "climbs up on a high bed," and meets his doctor who has a "white cloth tied round his head." He tells how the mask was put on and soon he was fast asleep. The next two drawings find him in the ward with other children and "Mummy has come back." The next shows "Daddy" carrying him out to his car the following morning, and the last, like the first, finds him in bed at home, finishing the story started in the first drawing. In this direct way the child learns what will happen to him when he has his tonsils taken out, and is psychologically prepared for the hospital experiences which are likely to cause trauma, such as the fear of being deserted by his parents and left at the hospital, and the necessary separation from the mother. No verbal preparation could possibly prepare the child so well for the experience.

No price, or as to whether the drawing book could be obtained by other doctors or institutions, came with the booklet, and so a letter of enquiry was sent to Dr. Luzzatti, Medical Director of the hospital in Oakland, suggesting it be made available to others. What we really wanted was to obtain copies to give to children in our own practice. Dr. Luzzatti replied that the response to the booklet had been so great, both inside and outside the community, it had been decided to put the booklet on sale, so it could be made available to institutions and doctors throughout the country. However, as of February 15, "final arrangements for publication had not been made."

Among the many hundreds of booklets and pamphlets with a specific purpose which have been called to the editor's attention over the years, we believe this booklet will accomplish its purpose as well, or even better, than any other we have seen. This may at first sight seem a rather lengthy review for a "child's drawing book" to appear in a medical journal. Every pediatrician who has seen over the years the emotional trauma produced in some children by a hospital experience, and the deep-seated fear of hospitals and doctors engendered in many following a tonsillectomy, will realize the significance and value of such a booklet.

B. S. V.

A Manual of Orthoptics. Julia E. Lancaster, Springfield, Ill., 1951, Charles C Thomas, Publisher, 199 pages. Price, $5.50.

This monograph can be divided for discussion into two parts, the first on orthoptic problems considering the theory and the second on techniques of training. The latter lends itself to a didactic approach and is a clear and concise presentation of the subject, very valuable for the orthoptic technician.

The philosophical preliminary is open to criticism for the very factor that makes the last half of the book so good in that there is a tendency to state as proved facts some controversial points. However, it expresses clearly one point of view with regard to the theory. This section should be read in conjunction with other books on the subject.

L. T. P.

Allergy in Relation to Pediatrics. Bret Ratner, M.D., St. Paul, Minn., 1951, Bruce Publishing Co., 228 pages. Price $3.75.

This is the report of a panel discussion of allergy held at a meeting of the American College of Allergists in 1949 of which Dr. Ratner was chairman. A group of sixteen allergists and pediatric allergists participated—each presenting a discussion of some particular phase. Among these, Peshkin discusses the evaluation of diagnostic tests for sensitization; Lewis Webb Hill, the significance of skin tests; McGee, allergy of the intestinal tract; Dees, neurological allergy; Deamer, environmental control; Glaser, office management of the allergic child; and Overall, drug therapy. The text thus presents an excellent summary of the various phases of allergy as related to pediatrics.

Editor's Column

PEDIATRICS PUT IN PART III NATIONAL BOARD EXAMINATION

AT LAST pediatrics is considered as a subject of major importance, and is to be included as such in the Part III examination of the National Board of Medical Examiners, which will be given in twenty-nine medical centers in June. This is the oral bedside examination given after the completion of a year of internship.

When the National Board was founded back in 1915, medicine, surgery, and obstetrics were considered major subjects and allotted three hours each, while pediatrics was not even included as a minor subject in a group of specialties as ophthalmology, otology, and dermatology. A committee of the Board appointed two years ago has revised Part III, and after a trial run the revised examination has been adopted and will go into general use in June. The examination now includes four major subjects—medicine, surgery, obstetrics, and pediatrics. In the new form it is a one-day six-hour bedside examination with two hours allotted to both medicine and surgery, and one hour each to pediatrics and obstetrics.

It was not until the mid-thirties, after a number of years of pressure on the part of a group of pediatricians, that a separate written examination was given in pediatrics in Part II of the National Board examination at the end of the fourth year of the medical school. Part I, in the basic sciences, is given at the end of the second year. Until now efforts to have pediatrics included as a major subject in Part III have been unsuccessful.

The inclusion of pediatrics as a major subject for examination on patients in the hospital brings a new group of responsibilities to the pediatricians and the pediatric hospital services. Men in the other three subjects are fully aware of their responsibilities and have cooperated over many years. But it is all new to the pediatrics group.

In each center there is a "Subsidiary Board" of the National Board, with a chief examiner, and a secretary who is the executive. All local details as to the hospitals where the examination is held, and the selection of local examiners are in the hands of the local board, subject to general uniform regulations of the National Board. The number of candidates presenting themselves for examination varies widely among the centers with several hundred in some of the larger metropolitan centers.

Approximately 1,500 candidates will be examined in June. If each examiner examines for six hours (six candidates), it will require the assistance of 250 pediatricians to give the examination. In some centers not more than three will be needed, while in others it may run as high as twenty-five or more. The selection of the examiners, as noted above, is the responsibility of the local subsidiary board. An honorarium is paid to each examiner by the National Board based on the number of candidates examined.

It has taken many years of continuing effort to raise pediatrics from a minor position in the medical cur-

riculum and practice to one in which it is recognized as one of the four major clinical subjects. Incidentally the "Study" of the Academy of Pediatrics which showed the amount of pediatrics in the daily work of the general practitioner played an important part in the inclusion of pediatrics as a major subject in Part III of the National Board examination.

Now that one of the goals that we as pediatricians have been striving for has been reached, it becomes the responsibility of the pediatricians and our pediatric hospital services to cooperate fully and wholeheartedly with the local subsidiary boards of the National Board. Otherwise the struggle will have been in vain and we could with justice be open to criticism.

THE PEDIATRIC SHIFT

PRIOR to 1900, with a few exceptions (Escherich in Vienna, Marfan and Nobecourt in Paris, Barlow and Still in London, Morquio in Montevideo, Bokáy in Budapest, Jacobi and Holt in New York, Rotch in Boston), pediatrics did not exist in the medical schools on this continent or in Europe. Not until 1911, when Pirquet transiently became professor of pediatrics or really not until 1912 when John Howland succeeded him, did pediatrics reach a university level at the Hopkins, and become worthy to be recognized as a separate entity by the curriculum committee. From 1912 to his death in 1926, Howland's thirty disciples became professors of pediatrics in many of the medical schools in the United States and abroad, and spread the gospel of university pediatrics. Similar awakenings and developments were occurring in other medical schools, under the leadership of Pirquet and Schick in Vienna, Finkelstein and Czerny in Berlin, Debré in Paris, Thursfield in London, and others.

At present, there are approximately 3,500 pediatricians certified by the American Board of Pediatrics, in addition to those who, though uncertified, confine their practice to children. However, in 1948 pediatricians provided only 11 per cent of child care in the United States in contrast to 75 per cent by general practitioners. Therefore, it is the duty of teachers in medical schools to study the pediatric shift and to provide the best modern instruction for the medical students who plan to enter general practice, as well as for those who are headed toward pediatrics. In fact, from the point of view of national child welfare, it is more important that the general practitioners understand pediatric methods, than it is to train pediatricians.

In addition to this rapid rise in university pediatrics and the increase in pediatricians, the shift in the content of pediatrics has been even more dramatic. From 1900 to 1920, pediatrics consisted largely of feeding babies, with the diagnosis and treatment of children's diseases as a side line. Starting in 1920, Marriott simplified infant feeding by the introduction of lactic acid evaporated milk, and the top-milk mixtures, the percentage formulas, Eiweis Milch, Butter-Mehlnahrung, and others, which required a pediatrician and a slide rule, soon disappeared.

The physician's time and energy which formerly were taxed by explaining complicated baby feedings to mothers now was available for immunizations and preventive pediatrics. In fact, by 1930, less than 50 per cent of their days (and nights)

were devoted to the diagnosis and treatment of sick children, and pediatric teachers taught more preventive medicine than did professors of public health; and properly so, for most of the decrease in mortality and the increase in the expected span of life have been due to the reduction in the deaths of infancy and early childhood by pediatricians. Brig. Gen. James Stevens Simmons, who was Chief of the Division of Preventive Medicine of the Army, stated that pediatricians were among his best health officers.

In 1930, before preventive measures, sulfonamide, and antibiotic therapy became so effective, the relative incidence of children's diseases was fairly stable and in the following order: respiratory, intestinal, cutaneous, neuropsychiatric, circulatory, metabolic, glandular, urologic, and orthopedic, with infections of all sorts predominating. By 1950, however, the incidence of children's diseases had entirely changed wherever there are pediatricians or children's clinics. This shift was primarily due to specific preventive measures. Pertussis, typhoid, and rickettsial vaccines, diphtheria and tetanus toxoids, and smallpox vaccination have almost eliminated those diseases. In 1930 when Duke Hospital was opened, diphtheria was responsible for 7 per cent of all of the pediatric hospital patients, but in 1949 and 1950 only three cases occurred. Immune serum globulin (human) has reduced the incidence and severity of measles, mumps, and rubella. Compulsory premarital and antenatal serologic tests and rapid treatment centers have made congenital syphilis, not only illegal, but also a rarity in comparison with its frequency before Thomas Parran started the campaign to eradicate it. Routine tuberculin tests and chest photofluorograms, the isolation of tuberculous patients in sanatoria, and, more recently, streptomycin therapy have reduced the incidence and mortality of childhood tuberculosis and pleurisy. Cod-liver oil, orange juice, thiamin, and niacin have reduced rickets, scurvy, beriberi, and pellagra chiefly to historic interest. Marked reduction in dysentery and diarrhea at Duke followed the widespread use of lactic acid evaporated milk for infant feeding.

Perhaps the most important cause of the reduction in pediatric hospital patients has been the almost universal and usually successful use of sulfonamide and antibiotic therapy,* either at home or by the attending physician, for any and all febrile infections, regardless of the diagnosis and often without one. Pneumonia, dysentery, empyema, erysipelas, mastoiditis, otitis media, pyelitis, septicemia, tonsillitis, etc., are cured without hospitalization and often before diagnosis. Certainly acute appendicitis with and without rupture, brain abscesses, and osteomyelitis have become rarer hospital admissions since the advent of chemotherapy. This practice of giving sulfonamides, penicillin, streptomycin, aureomycin, chloramphenicol, etc., for several days without examining the patient, and then trying to diagnose those in whom the treatment is unsuccessful is appalling from the point of view of pediatric instruction, though it simplifies the practice of medicine. Pediatric instructors should realize that, regardless of arguments to the contrary,

*Cost at Duke Hospital during the past six months:

Penicillin	$20,000.00
Streptomycin	9,263.00
Terramycin	7,865.00
Aureomycin	3,574.00
Chloramphenicol	2,563.00

this practice will be continued as it usually is effective and rarely does harm.

From a teaching point of view, the remaining pediatric conditions should be divided into those which still require hospitalization and those which should be treated as ambulant in a physician's office or in an out-patient clinic. When separated in this way, it will be readily seen that fewer pediatric hospital beds will be needed and that more space, a larger percentage of the pediatric teaching hours, and better instruction are necessary in pediatric out-patient clinics, both public and private. If more visiting nurses were available for home care, an even larger percentage of pediatric patients could be treated as out-patients and the number of pediatric hospital beds could be reduced even further. Out-patient teaching is more important and more desirable than that on the wards—a complete reversal of the usual concept.

The most frequent conditions which still require hospitalization at Duke are: abnormalities of the newborn, including premature infants, surgical conditions, cancer, which is now the second ranking cause of death from disease in children, congenital heart disease, rheumatic fever which kills so many children between the ages of 5 and 14 years, and last but not least, the increasing tide of accidents, the greatest killer of all. Practically everything else in pediatrics can be, and should be, treated in an out-patient clinic.

Eventually, children's hospitals should be empty, except for newborn and premature infants, the ill children of working mothers, accidents, and unpreventable surgical operations. However, home care and delay are still dangerous for children with stiff necks, "acute abdomens," and respiratory obstructions, especially in those under 2 years of age.

Keeping children out of hospitals and treating them in a physician's office or out-patient clinic not only is a great psychologic benefit to the mother and child but the financial saving is enormous, regardless of whether the child's parents or the taxpayers or university endowments pay the bill.

In addition, pediatric departments must devote greater and more interesting efforts to teaching future general practitioners and pediatricians more about well children through the examination of school children, child guidance conferences, feeding clinics, and seminars on nutrition with the dietetic department. Family physicians or pediatricians are tending to be occupied less and less with physical disease, and more and more with growth, development, behavior problems, school and social development. Parents and physicians are becoming increasingly aware of the importance of the child's total development and adjustment. In this field of preventive psychiatry and psychosomatic medicine, social workers, nurses, teachers, pediatricians, psychologists, psychiatrists, and other physicians must work together, and the ideal place is in the out-patient clinic or physician's office. In other words, the title of the Department of Pediatrics should be changed to the Department of Child Life as at the University of Edinburgh.

W. C. DAVISON.